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RELATION OF THE HEMOLYTIC STREPTOCOCCUS TO RHEUMATIC FEVER

IV. Effect of Streptococcic Spreading Factor in Rheumatic Patients and Others

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IN THE natural history of rheumatic fever, there are two sets of observations, the epidemiologic[1] and the immunologic,[2] which bear some implication as to a specific etiologic agent. The data in both these fields of observation point to the hemolytic streptococcus as having some causal relation to the disease, although they offer no hint of a possible mechanism by which the hemolytic streptococcus might cause the phenomena of rheumatic fever. In the immunologic field, earlier analytic work on this question, as well as current work in these laboratories,[3] has been reviewed elsewhere.

Among the biochemical effects which might be caused by the streptococcus, the possible role of streptococcic hyaluronidase in the pathogenesis of rheumatic fever has been the subject of recent speculation.[4] This speculation has been based on three propositions: (1) Rheumatic fever is a disease of hyaline connective tissue; (2) hyalu-

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1. Paul, J. R., and others: The Epidemiology of Rheumatic Fever and Some of Its Public Health Aspects, ed. 2, New York, Metropolitan Life Insurance Company, 1943.

2. Harris, T. N.: Studies in the Relation of Hemolytic Streptococcus to Rheumatic Fever: I. Review of Serologic Literature, Am. J. Dis. Child. **76**:411 (Oct.) 1948.

3. (*a*) Harris, T. N.: Studies in the Relation of the Hemolytic Streptococcus to Rheumatic Fever: II. Fractionation of the Hemolytic Streptococcus by High Speed Centrifugation, J. Exper. Med. **87**:41-56 (Jan.) 1948; (*b*) III. Complement-Fixation Tests Versus Streptococcal Nucleoproteins in the Sera of Patients with Rheumatic Fever and Others, ibid. **87**:57-70 (Jan.) 1948.

4. Meyer, K.: The Biological Significance of Hyaluronic Acid and Hyaluronidase, Physiol. Rev. **27**:335-359 (July) 1947.

ronic acid, which characterizes hyalin, is susceptible of enzymic digestion (depolymerization) by hyaluronidase,[5] and (3) the hemolytic streptococcus is one of the bacterial species which produces this enzyme.[6]

Since the discovery of the streptococcic spreading factor by Duran-Reynals,[7] evidence has been accumulated that hyaluronidase is at least an integral and essential part of the various spreading factors which have been identified.[8] The spread of indicator dyes in the tissues under the influence of spreading factors, such as that elaborated by the streptococcus, would therefore provide a measure of the susceptibility of those tissues to the effect of hyaluronidase. One therefore could detect an extraordinary susceptibility of the hyaluronic acid of the tissues of rheumatic subjects to depolymerization by hyaluronidase by observing the rate of spread of a standard dye-hyaluronidase mixture in the skin of this group of patients as compared with the rate of spread in control subjects.

Additional stimulus was given to this study by the work of Guerra,[9] who reported that hyaluronidase causes far greater spread of indicator dyes in the skin of rheumatic subjects, both active and quiescent, than in normal subjects, with the accompaniment of massive inflammatory changes, and that this effect is neutralized by salicylates. Considerable emphasis was laid by Guerra on the recently renewed suggestion[10] that salicylates are a specific antirheumatic agent. The conclusions drawn were that the mechanism of rheumatic fever involves the degradation of hyaluronic acid by hyaluronidase, and that the mechanism of the specific antirheumatic effect of salicylates is the inhibition of this enzyme. As a matter of fact, this revival of an

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5. Meyer, K.; Dubos, R., and Smyth, E. M.: The Hydrolysis of the Polysaccharide Acids of Vitreous Humor, of the Umbilical Cord, and of Streptococcus by the Autolytic Enzyme of Pneumococcus, J. Biol. Chem. **118**:61-78 (March) 1937.

6. Meyer, Dubos and Smyth.[5] Meyer, K.; Hobby, G. L.; Chaffee, E., and Dawson, M. H.: The Hydrolysis of Hyaluronic Acid by Bacterial Enzymes, J. Exper. Med. **71**:137-146 (Feb.) 1940.

7. (*a*) Duran-Reynals, F.: Exaltation de l'activité du virus vaccinal par les extraits de certains organes, Compt. rend. Soc. de biol. **99**:6-7 (June) 1928. (*b*) Chain, E., and Duthie, E. S.: A Mucolytic Enzyme in Testis Extracts, Nature, London **144**:977-978 (Dec. 9) 1939.

8. Chain and Duthie.[7b] Meyer, K.; Chaffee, E.; Hobby, G. L., and Dawson, M. H.: Hyaluronidases of Bacterial and Animal Origin, J. Exper. Med. **73**: 309-326 (March) 1941.

9. Guerra, F.: Hyaluronidase Inhibition by Sodium Salicylate in Rheumatic Fever, Science **103**:686-687 (June 7) 1946; The Action of Sodium Salicylate and Sulfadiazine on Hyaluronidase, J. Pharmacol. & Exper. Therap. **87**:193-197 (July) 1946.

10. Coburn, A. F.: Salicylate Therapy in Rheumatic Fever: A Rational Technique, Bull. Johns Hopkins Hosp. **73**:435-464 (Dec.) 1943.

earlier suggestion [11] of specific antirheumatic action by salicylates has met with several refutations [12] supported by experimental evidence, and the entirely nonspecific effect of salicylates in denaturing enzymes and other proteins has been observed frequently.[13]

Although the inhibition of the spreading effect of hyaluronidase by salicylates has been confirmed,[14] evaluation of the data presented by Guerra and of the conclusions drawn from them with regard to rheumatic fever is difficult because of the large doses of hyaluronidase-containing material injected and the intense inflammatory reactions produced by these injections. In the presence of the intense vascular activity and edema accompanying inflammation of the severity described in the papers mentioned, it is difficult indeed to ascribe the spreading and disappearance of dye to enzyme activity alone. Again, if the pathogenesis of rheumatic fever depends on increased susceptibility of the tissues to hyaluronidase, as compared with that of normal tissue, it should not require massive doses of the material to elicit this difference.

In planning the present study, it was assumed that if the possible relation of the hemolytic streptococcus to rheumatic fever is mediated by hyaluronidase, the amounts of the streptococcic enzyme involved must be minimal, since no frank streptococcic infection can be identified during this disease. Accordingly, the present study was planned to investigate a possible role of streptococcic hyaluronidase in rheumatic fever by determining whether the tissues of the rheumatic sub-

11. Lees, D. B.: The Treatment of Some Acute Visceral Inflammations, Brit. M. J. **2**:1318-1322, 1903.

12. Murphy, G. E.: Salicylate and Rheumatic Activity: An Objective Clinical-Histologic Study of the Effect of Salicylate on Rheumatic Lesions, Those of Joints and Tendon Sheaths in Particular, Bull. Johns Hopkins Hosp. **77**:1-42 (July) 1945. Harris, T. N.: The Failure of Massive Salicylate Therapy to Suppress the Inflammatory Reaction in Rheumatic Fever, Am. J. M. Sc. **213**: 482-487 (May) 1947.

13. Anson, M. L., and Mirsky, A. E.: The Equilibria Between Native and Denatured Hemoglobin in Salicylate Solutions and the Theoretical Consequences of the Equilibrium Between Native and Denatured Protein, J. Gen. Physiol. **17**:399-408 (Nov.) 1934. Holden, H. F.: The Denaturation of Haemoglobin, Australian J. Exper. Biol. & M. Sc. **15**:43-48 (March) 1937. Bawden, F. C., and Pirie, N. W.: The Effects of Alkali and Some Simple Organic Substances on Three Plant Viruses, Biochem. J. **34**:1278-1292 (Sept.) 1940. von Euler, H., and Ahlström, L.: Der Einfluss von Na-Salicylat auf Enzymsysteme, Ztschr. f. physiol. Chem. **279**:175-186 (July) 1943. Best. R. J.: Thermal Inactivation of Tomato Spotted Wilt Virus, Australian J. Exper. Biol. & M. Sc. **24**:27-31 (March) 1946.

14. Dorfman, A.; Reimers, E. J., and Ott, M. L.: Action of Sodium Salicylate on Hyaluronidase, Proc. Soc. Exper. Biol. & Med. **64**:357-360 (March) 1947.

ject are abnormally susceptible to the action of a spreading factor of streptococcic origin in quantities which represent only a small number of minimally effective units, as determined in the normal subject.

METHODS AND MATERIALS

Preparation, Purification and Sterilization of the Hyaluronidase.—The source of streptococcic spreading factor was a strain of group A hemolytic streptococcus, H 44, originally supplied by Dr. Karl Meyer, of New York. In other studies on hyaluronidase in this laboratory,[15] it had been found that the broth supernate of cultures of hyaluronidase-producing organisms furnished a more convenient source of the enzyme than extracts of the bacterial cells themselves. In order that the amount of nonhyaluronidase protein to be introduced into the skin of experimental subjects might be minimized, this strain of streptococcus was grown in a protein-free medium, the culture supernate of which was then collected, concentrated and purified with respect to the spreading factor.

The protein-free medium was prepared as follows: Dehydrated dextrose broth (Difco), 175 Gm., was dissolved in 375 cc. of distilled water, the resulting concentration being twenty times that used in preparing ordinary medium. The concentrated solution was distributed in 75 cc. amounts in cellophane bags (Visking sausage casing), 27/32 inch (2.14 cm.), each of which was suspended in the upper part of a 1,000 cc. graduated cylinder filled with distilled water. Dialysis, at 4 C., was allowed to continue overnight, with occasional inversion of the bags, after which the bags were removed from the cylinders and the dialysates were pooled. To each 2.5 liter batch of this pooled material was added 500 cc. of a dialysate of Pfanstiehl peptone (20 Gm. in 50 cc. of distilled water, dialyzed overnight against 10 volumes of water). The resulting medium, which was a clear yellow, was sterilized in 4 liter flasks in the autoclave at a pressure of 20 pounds per square inch and a temperature of 115 C. for thirty minutes. The medium prepared in this manner had a p_H of 6.5. A molar solution of sodium hydroxide was therefore added in order to elevate the p_H to about 7.2. It was usually found that the addition of 2 cc. of molar solution of sodium hydroxide per liter of medium was sufficient. Finally, 300 cc. of a molar solution of sodium bicarbonate, sterilized by filtration, was added, as well as a small quantity of phenolsulfonphthalein U. S. P. (phenol red). The medium, now ready for inoculation, had a p_H of approximately 7.8.

In order that a low concentration of oxygen should be maintained in the medium, the medium was inoculated within a few hours after being autoclaved. The inoculum was prepared by seeding 300 cc. of ordinary dextrose broth (Difco) with 300 cc. of an overnight culture of H 44 streptococci, and incubating this culture for six hours. The bacterial sediment was then collected by centrifugation and used as seed for the culture in the 4 liter flask.

After incubation for sixteen hours at 37 C., the culture was removed from the incubator and its p_H readjusted. The supernate was then collected by centrifugation and pooled with supernates of other (3 liter) cultures grown for the same preparation of spreading factor. The combined supernates were distributed in 700 cc. amounts in wider cellophane bags, which were hung on a wooden rack before a 26 inch (66 cm.) electric fan for concentration by pervaporation. After

15. Harris, T. N., and Harris, S. I.: Studies in Relation of the Hemolytic Streptococcus to Rheumatic Fever: V. Antihyaluronidase Titres in Sera of Patients with Rheumatic Fever and Others, Am. J. M. Sc. **217**:174-186 (Feb.) 1949.

sixteen hours of pervaporation, during which period the temperature of the material remained at about 12 C., the contents of the bags, now concentrated approximately tenfold, were pooled and subjected to vigorous centrifugation (thirty minutes at 5,000 revolutions per minute) in order to remove any bacterial cells which might not have been removed in earlier procedures. This concentrate was dialyzed overnight against running tap water and then against distilled water, after which the volume was further reduced by pervaporation for six hours at 12 C. The pooled concentrates were then desiccated from the frozen state, and the dried protein was stored at —10 C., not in vacuo.

Further steps in purification with respect to spreading factor were adapted from Madinaveitia's [16] purification of testicular spreading factor. One gram of the crude preparation of spreading factor was dissolved in 100 cc. of distilled water. Twenty-five grams of ammonium sulfate was added and the resulting precipitate discarded. Another 30 Gm. of the salt was added, and the precipitate was collected, redissolved, dialyzed overnight against 18 liters of distilled water and then desiccated. The yield was 240 mg. of material, with a spreading potency approximately twice as high with reference to dry weight as the starting material, according to tests which are to be described later in this paper.

After pilot batches of streptococcic proteins containing spreading factor had been prepared, a single large batch was prepared and purified, as described. This preparation was stored at —10 C., not in vacuo, and was used for all the experiments to be described.

Sterilization of the preparation of spreading factor for injection presented additional problems, since sterilization of an enzyme by heat was impossible. It was found that almost all the spreading potency of the preparation was lost on filtration through a Seitz filter, and even filtration through sintered glass resulted in a loss of about half the potency. It was found possible, however, to expose a solution of the material to ultraviolet rays for a period sufficiently long to assure its sterilization bacteriologically, without materially affecting the enzymic activity. In practice, a solution of the spreading factors preparation, in a concentration of 1 mg. per cubic centimeter, was dispensed into Petri plates in a shallow layer and exposed to radiation while being agitated.[17] After ten minutes of irradiation, the plates were covered and their contents pooled and dispensed in 2 cc. quantities into sterile vials. Desiccation from the frozen state was then carried out, with sterile precautions. By this procedure we prepared a number of vials, each containing 2 mg. of a dry, sterile preparation of streptococcic proteins possessing spreading factor. These vials were stored at —10 C. For use in a test, the hemoglobin solution used as indicator was introduced directly into the vial as solvent for the desiccated hyaluronidase.

Assay of the Hyaluronidase.—The streptococcic hyaluronidase thus prepared was assayed in vitro, in terms of its ability to depolymerize hyaluronic acid in solution, and in vivo, in terms of its potency as a spreading factor. The in vitro test was done by adapting the mucin clot-prevention test of Robertson and his

16. Madinaveitia, J.: Diffusing Factors: Concentration of Mucinase from Testicular Extracts and from Crotalus Atrox Venum, Biochem. J. **35**:447-452 (April) 1941.

17. Henle, W., and Henle, G.: Interference Between Inactive and Active Viruses of Influenza: I. The Incidental Occurrence and Artificial Induction of the Phenomenon, Am. J. M. Sc. **207**:705-717 (June) 1944.

associates.[18] This test depends on the fact that native hyaluronic acid, in the presence of protein, is precipitated by acid into a single fibrous "mucin" clot, whereas the depolymerized form, in these circumstances, yields a flocculent precipitate.[18a] In the test as done here,[15] 0.4 cc. of the redissolved preparation of hyaluronidase was incubated at 37 C. for twenty minutes with 0.4 cc. of potassium hyaluronate solution which contained 0.4 mg. of the hyaluronate and 10 per cent of normal horse serum. The tubes were then chilled suddenly to interrupt the action of the enzyme, and 0.2 cc. of twice normal acetic acid was added to each tube. When the tubes were shaken vigorously, a mucin clot appeared in the tubes in which there was no hyaluronidase, or not enough to digest the hyaluronic acid present, whereas a flocculent precipitate was taken as a positive indication of the presence of enzyme in demonstrable quantity. By this test, it was found that 6 micrograms of the desiccated streptococcic proteins contained enough hyaluronidase to cause digestion of the 0.4 mg. of hyaluronic acid.

The in vivo assay of this material for its potency as a spreading factor involved the choice of an indicator dye. Because human subjects were to be used in the experiments, it was necessary to use an indicator of spreading which would be innocuous and which would disappear from the skin rather soon after the experiment. Accordingly, human hemoglobin was the indicator used.

Sterile group O human blood was obtained through the courtesy of the Philadelphia Serum Exchange. The erythrocytes were washed several times with sterile isotonic sodium chloride solution U. S. P., after which the cells were repacked by centrifugation and shaken in 1 volume of sterile distilled water. Time was allowed for hemolysis; then successive centrifugations were performed until no further sedimentation of the stromas of erythrocytes could be noted. One-fortieth volume of a sterile 17 per cent solution of sodium chloride was added to restore isotonicity, and the solution of hemoglobin was stored at 4 C. while the usual tests for bacterial sterility were being performed.

In the assay of the spreading factor, and in the experiments to be reported, cognizance was taken of the importance of the interstitial pressure in the distended skin at the site of injection.[19] Accordingly, every effort was made to assure constancy of the volume of the dye-spreading factor injected, and, for the reasons stated in the following discussion, the volume injected was maintained at 0.05 cc., which was the smallest practicable volume. Injections were made with a 0.25 cc. tuberculin syringe and a 27 gage needle.

The desiccated preparation of spreading factor was dissolved directly into the solution of hemoglobin, and further dilutions were made with the same preparation of hemoglobin, so that the intensity of color was constant in all the solutions injected. Measurements of the patch discolored by hemoglobin were made immediately after the injection; and thereafter at ten, twenty and sixty minutes and at two hours. The longest axis of the area of discoloration was measured, as well

18. Robertson, W. V.; Ropes, M. W., and Bauer, W.: Mucinase: A Bacterial Enzyme Which Hydrolyzes Synovial Fluid Mucin and Other Mucins, J. Biol. Chem. **133**:261-276 (March) 1940.

18a. Seastone, C. V.: The Virulence of Group C Hemolytic Streptococci of Animal Origin, J. Exper. Med. **70**:361-378 (Oct.) 1939.

19. Hechter, O.: Studies on Spreading Factors: I. The Importance of Mechanical Factors in Hyaluronidase Action in Skin, J. Exper. Med. **85**:77-97 (Jan.) 1947.

as the one perpendicular to it. The area of the patch was then obtained by multiplying the product of the lengths of the two axes, in millimeters, by 0.785, since the area of an ellipse is given by the expression

$$A = \frac{\pi D d}{4}$$

where D and d are the lengths of the major and minor axes, respectively. The area of discoloration at the end of one hour was used in most of the calculations. For a given material injected, the rate of spread, in square millimeters per hour, was taken as the difference between the area at the site of that injection and the corresponding area at the site of injection of hemoglobin. Female albino rabbits were used for preliminary assays. Shaving was done on the evening before the day of the experiment, in order to avoid local irritation of the skin at the time of injection.

In comparing the potency of different preparations, experiments were always arranged so that both or all preparations were represented on a given rabbit, usually in anatomic symmetry. Thus successive dilutions of a given preparation were injected in a row parallel to the spine along one side of the back of the animal, the last of the row being the injection of hemoglobin alone, while the preparation to be compared with it was injected in similar dilutions in a similar row on the other side of the spine, terminating, again, in a control injection of hemoglobin alone. Usually, at least 3 rabbits were used in such a comparative assay.

Clinical Material.—The patients studied were in the wards of the Children's Hospital of Philadelphia, the Philadelphia General Hospital and the Children's Seashore House, Atlantic City, N. J. Of these, the patients with rheumatic fever were among those under long term clinical observations, as described elsewhere,[3b] in the course of an investigation of the etiology of rheumatic fever. All the patients were white children, between the ages of 6 and 14 years in various stages of activity of the rheumatic process. (An attempt to employ fluorescein as indicator and ultraviolet light as illuminator in Negro children was abandoned because of technical difficulties.) Children hospitalized for reasons entirely unrelated to rheumatic fever, so far as known, and a few normal children, were used as controls.

RESULTS

Assay and Standardizations.—Preliminary assays of the spreading potency of the preparation of streptococcic hyaluronidase were performed on rabbits. A typical set of data, showing the spread of indicator in the presence of various amounts of the streptococcic preparation, are given in chart 1.

The curves in chart 1 show that definite differences in spreading effect are produced by tenfold steps in the amount of hyaluronidase present, and that the minimal dose of this preparation of streptococcic proteins which produces definite spreading in the skin of the rabbit is of the order of 1 microgram. Titration of the spreading effect in successive twofold dilutions of the hyaluronidase, such as was necessary to guide the steps of purification and sterilization, was successful only in some experiments because of the technical difficulties involved. This chart shows also that the agent which caused spread-

ing was destroyed at 100 C., as would be expected in the case of an enzyme, and that there was considerable loss of activity on sterilization by Seitz filtration.

Standardization in the Human Subject.—Since it was the purpose of this investigation to study a possible relation of streptococcic hyaluronidase to the pathogenesis of rheumatic fever, it was considered important, for reasons which will be discussed, to use a relatively small amount of the enzyme, and to cause as small a change as possible in the interstitial pressure of the tissue injected.

In order to determine the minimal effective dose of the preparation of streptococcic hyaluronidase in the human skin, titrations were

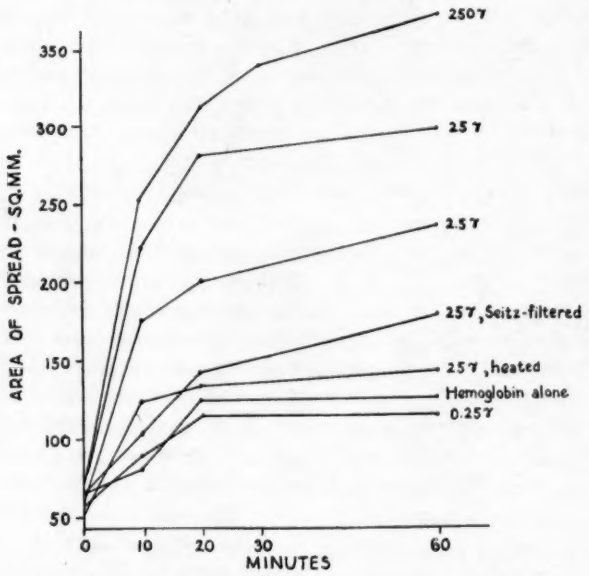

Chart 1.—Spreading in the rabbit's skin caused by various amounts, expressed in micrograms, of hyaluronidase-containing streptococcic proteins. The effect of heating and Seitz filtration on the activity of the hyaluronidase is shown.

carried out on normal children and in those hospitalized for causes entirely unrelated to rheumatic infection. Such titrations showed that the human skin is somewhat less susceptible to the streptococcic spreading factor than the skin of the rabbit, the threshold dose for the human skin being on the order of 10 micrograms of the partly purified streptococcic preparation employed.

Finally, it was necessary to determine the volume at which the injections would be made in the clinical experiments, since it has been noted by previous investigators that the pressure created at the site of injection has considerable influence on the observed rate of spread

of the indicator.[20] Some data have, in fact, shown that hyaluronidase applied to incisions on the surface, where there is no change from the physiologic interstitial pressure, does not cause an increased spread of the indicator dye at all. Again, it has been reported that the volume of the injected mass may in some cases, through its effect on the interstitial pressure, be a greater factor in affecting the rate of spread than the number of units of spreading factor injected.[19]

Although some distortion of the interstitial pressure of the skin was necessary for the measurement of the effect of hyaluronidase in vivo, and was, indeed, unavoidable because the material was injected intradermally, it was desirable to minimize the extent of this change from the normal state of the tissues. Accordingly, experiments were

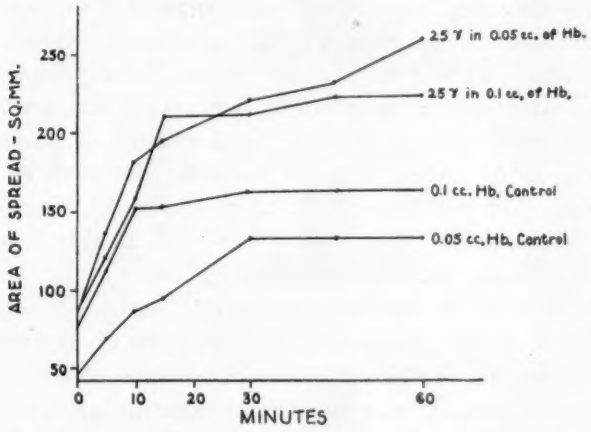

Chart 2.—Typical experiment on human subject, showing effect of the volume injected on the demonstration of streptococcic spreading factor.

conducted to determine the minimal volume which could be accurately injected and which would cause sufficient distention of tissue to allow demonstration of the spreading effect. In such experiments the amount of hyaluronidase preparation and the concentration of hemoglobin were kept constant, and the volume injected was varied. Chart 2 shows the results of a part of one such experiment, in a human subject, in which 25 micrograms of the preparation of hyaluronidase was injected in total volumes of 0.05 and 0.1 cc., respectively, of hemoglobin solution.

It is seen in chart 2 that this constant amount of enzyme affords as effective a demonstration of spreading when used in 0.05 cc. of

20. McClean, D.: The Influence of Testicular Extract on Dermal Permeability and the Response to Vaccine Virus, J. Path. & Bact. **33**:1045-1070 (Oct.) 1940.

indicator solution as in the larger volumes tested. Accordingly, this volume was used in the clinical experiments to be reported.

Clinical Experiments.—In early clinical experiments an attempt was made to inject the hyaluronidase at several concentrations. It was found, however, that twofold steps of dilution did not yield satisfactorily consistent differences in spread. Wider differences in such titrations were not feasible because it was found that substantially larger amounts of the streptococcic proteins than minimal doses for satisfactory demonstration of the spreading effect gave rise to mild, local inflammatory responses at the site of injection. These were in evidence later on the day of the injection and on the following day, and often disappeared within forty-eight hours. It was assumed that this transient inflammation was due to some protein or proteins produced by the streptococcus and not removed from the spreading factor by the single step in purification. In order to observe this toxic or allergic effect without interference by the hemoglobin dye, injections were made of the appropriate dilution of the preparation of streptococcic spreading factors in buffered solution of isotonic sodium chloride. In many experiments all subjects who received injections of spreading factor and hemoglobin received parallel injections of the spreading factor alone. The latter were read as skin tests, twenty-four and forty-eight hours after injection.

Finally, in order to test the assumption that the observed difference in rate of spread of dye between injections of hemoglobin alone and those of hemoglobin plus the spreading factor was due to enzyme in the bacterial preparation, a number of experiments were performed in which the subjects were given parallel injections of the streptococcic preparation which had been placed in a boiling water bath for twenty minutes before the addition of hemoglobin.

Four groups of observations were made:

Comparison of Rate of Spread of Indicator in Normal and Rheumatic Subject: Measurements of the rate of spread of the hemoglobin were made on 61 children. These included 17 patients with active rheumatic disease, 16 patients with quiescent rheumatic condition and 28 control subjects. Each experiment included both normal and rheumatic subjects within the same group, in order to assure valid comparisons throughout the study. In a given experiment, the dilutions of spreading factor in hemoglobin solution were injected with an accompanying injection of hemoglobin alone. Of the two additional injection materials mentioned, that is, the solution containing spreading factor alone and the preparation containing hemoglobin with heated spreading factor, one or both were included in each experiment.

Since typical curves showing the spread due to hyaluronidase have been presented (charts 1 and 2), the results of the clinical experiments will be presented as the amount of spread, in square millimeters, in one hour, without reproduction of additional curves. The distribution of these rates of spread among the three clinical groups is shown in chart 3.

Chart 3 shows that amounts of streptococcic hyaluronidase which had a small, but definite, spreading effect in control subjects induced

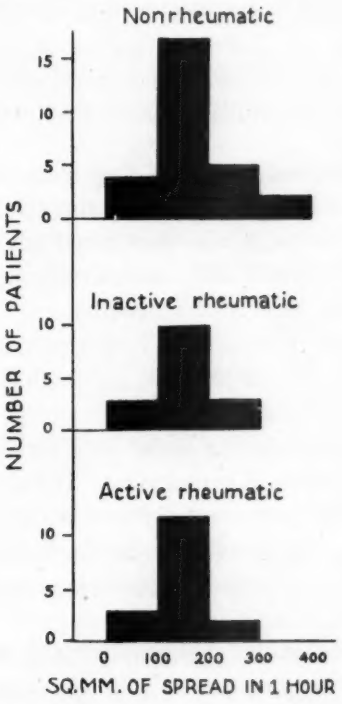

Chart 3.—Extent of spreading expressed in square millimeters at the end of one hour, caused by injection of 25 micrograms of hyaluronidase-containing streptococcic proteins in rheumatic and nonrheumatic subjects. The height of each column represents the number of children showing a degree of spread corresponding to the range indicated.

the same rates of spread in patients with active or inactive rheumatic fever, with essentially the same frequency, indicating that the tissue of rheumatic subjects has no unusual susceptibility to this material.

Inflammatory Reaction Due to Streptococcic Proteins Injected: In view of the considerations discussed in the introduction of this paper, it was especially desirable to study the reactions of the skin to the injected bacterial proteins. The reaction, when it occurred, resembled a positive skin test of the tuberculin type except that the intensity of

inflammation was often maximal twenty-four hours after injection and had receded or disappeared entirely twenty-four hours later. It was found that on the day after injection the hemoglobin in the spreading test area had so thinned out because of the spreading phenomenon that the site of injection could be read as a skin test. Repeated comparisons between this area and the site of injection of the spreading preparation without hemoglobin showed very little difference between the two on the day after the injections. Therefore, in later experiments, the same injection was used for measurement of spread on the first day and for the reaction of the skin to the streptococcic proteins on the following days.

The intensity of the inflammatory reaction to the material injected in the skin did not differ appreciably in rheumatic patients from that in control subjects.

Association of Observed Spread of Dye with Streptococcic Enzyme: Since there was some inflammatory response to the streptococcic proteins in the injected tissue, it was considered advisable to demonstrate that the spreading of the indicator, as observed, was due to an enzyme, and not to the vascular effects of inflammation. Accordingly, in some experiments, the usual injections of hemoglobin and spreading factor were controlled by parallel injections, in which the streptococcic proteins, dissolved in a small amount of isotonic solution of sodium chloride, were placed in a boiling water bath for twenty minutes before being added to the solution of hemoglobin. It was found that, as in the case of the typical experiment in rabbits shown in chart 1, such heating inactivated the spreading factor. A lesser degree of heat, 56 C. for ten minutes, reduced the spreading potency to approximately half the original activity.

As a final corollary of the evidence that the observed spreading of dye was due to the enzyme, and not to an inflammatory reaction to streptococcic proteins, it was necessary to show that the heating which had inactivated the spreading effect had not denatured the accompanying streptococcic proteins to the point of not eliciting an inflammatory reaction in human skin. Accordingly, contents of two vials of the streptococcic preparation were dissolved in physiologic isotonic solution of sodium chloride rather than hemoglobin solution. One vial was heated in the manner previously described, and then the contents of both vials were used in parallel skin tests on 6 subjects who showed positive cutaneous reactions to this preparation. The skin tests were made with the use of several concentrations of the protein in order to facilitate the detection of any difference in reactivity of a given subject to the natural and the heated preparations. The results of this experiment are shown in the accompanying table.

The table shows that heating to 100 C. for twenty minutes caused no significant diminution in the degree of inflammatory reaction elicited by the streptococcic proteins.

Relation of Circulating Antihyaluronidase to the Effect of Streptococcic Spreading Factor: Since titrations of anti-streptococcic-hyaluronidase in serum were being performed in these laboratories at the time, parallel experiments were carried out to ascertain whether there was any relation between the titer of neutralizing humoral antibodies to hyaluronidase and the effect of streptococcic spreading factor. No relation could be found between the two. The minimal effective concentration of streptococcic spreading factor was not appreciably neutralized in the skin by relatively large amounts of circulating hyaluronidase. Since there is little doubt of the close association, if not identity, of the

Dermal Sensitivity to the Hyaluronidase-Containing Preparation of Streptococcic Proteins Before and After Heating to 100 C for Fifteen Minutes

	Area of Inflammatory Reaction, Sq. Cm.			
	After 24 Hours		After 48 Hours	
Patient	Unheated	Heated	Unheated	Heated
M. C.	2.8	2.2	2.5	3.1
M. W.	5.5	5.5	7.6	8.7
J. G.	7.5	8.0	17.2	11.3
G. F.	5.5	4.5	10.4	7.7
J. C.	4.0	2.5	3.8	3.3
N. D.	6.7	5.6	11.6	11.0

two enzymes, it is likely that this lack of inhibition was due to failure of contact between circulating antibodies and intradermally injected material during the short period of observation.

An analogous situation in the case of nonspecific inhibitors of the spreading reaction has been noted by Hechter and Scully.[21]

COMMENT

If the hemolytic streptococcus is involved in the pathogenesis of rheumatic fever by means of hyaluronidase, two possible mechanisms must be considered. First, the tissues of the rheumatic patient might be subjected to streptococcic hyaluronidase in an unusual concentration or for unusually long periods of time, such as might be the case if a hidden focus of streptococci persisted in the body and continued to produce hyaluronidase. Second, the tissues of the rheumatic subject might be peculiarly susceptible to the enzyme as compared with the

21. Hechter, O., and Scully, E. L.: Studies on Spreading Factors: II. The Effect of Serum upon Hyaluronidase Spreading Activity, J. Exper. Med. **86**:19-28 (July) 1947.

tissues of normal subjects. The first of these two possibilities has been approached elsewhere [15] in a study of neutralizing antibodies to streptococcic hyaluronidase in the serums of rheumatic patients. The other possibility is examined in the present study.

This investigation was planned in such a way as to favor the demonstration of any increased susceptibility to hyaluronidase which might exist in the tissues of the rheumatic subject. Thus, the dose of spreading factor used in the standard tests was one which caused only a moderate rate of spread in normal subjects, in order to facilitate the recognition of any greater rate of spread in the skin of rheumatic subjects. Also, this small dose was better suited to the present study because the streptococcic proteins injected were not in such high concentration as to cause violent inflammatory reactions and thus confuse the results by vascular phenomena. Finally, it was considered more realistic, in terms of present knowledge of rheumatic fever, to use such small amounts of the enzyme, since streptococcic hyaluronidase, if it is involved in the pathogenesis of rheumatic fever, would certainly be present in the tissues in extremely small quantities, vigorous bacteriologic research having failed to demonstrate frank streptococcic infection during acute rheumatic fever. For this reason, also, the volume of material injected was kept at a minimum, since it is extremely doubtful whether interstitial pressures might exist at the site of rheumatic inflammation comparable to those created by intradermal injections.

Despite these favorable conditions, the data presented here give no evidence of increased susceptibility of the skin of rheumatic subjects to streptococcic spreading factor. This conclusion is directly opposed to the results of Guerra's study.[9] It is felt that the results of the present study are the more applicable to the problem of rheumatic fever, for several reasons. First, as already mentioned, the smaller doses used here are more likely to be the ones involved, if streptococcic hyaluronidase is related to the pathogenesis of rheumatic fever. Second, Guerra's results were obscured by the effects of massive inflammatory reactions, with all the changes in vascular activity and local fluid balance that these imply. These inflammatory reactions were, in all probability, related not to the spreading factor but to toxic or allergic reactions to accompanying proteins in the preparations used. Finally, in this study, the experiments included controls to prove that a substance with the heat lability of an enzyme, rather than the vascular reactions of inflammation, was responsible for the spread observed. Thus it was shown that the agent of the spreading effect was heat labile, but that similar heating did not affect the activity of the streptococcic proteins in evoking an inflammatory reaction in the skin.

It may be in point to indicate a conceivable mechanism by which a spread of dye involving the vascular reactions of inflammation might be greater in rheumatic subjects than in normal children. Guerra did not state whether the violent inflammatory reactions observed, with increased spread of dye, followed the injection of testicular or streptococcic preparations containing spreading factor. If the latter, the response may well be explained on the basis of greater hypersensitivity of rheumatic subjects as a group to the preparation of streptococcic proteins used in that study, as compared with normal subjects. Such differences have been observed for various preparations of streptococcic proteins, since the early studies of Collis, Sheldon and Hill [22] and Keefer and associates,[23] but never with a constancy or intensity which would imply that a specific allergen of rheumatic fever was included in the preparation used for skin testing. In all probability, this phenomenon is due to the greater contact between the rheumatic host and the hemolytic streptococcus, just as the serologic titers of rheumatic patients as a group to a variety of streptococcic antigens are higher than those found in the normal population of the same age group.

SUMMARY

Intradermal injections of as small a volume as 0.05 cc. cause sufficient intradermal pressure to permit demonstration of the spreading effect of constant amounts of streptococcic hyaluronidase.

Patients with active or quiescent rheumatic fever do not show an unusual susceptibility to streptococcic spreading factor (hyaluronidase) as compared with control subjects.

The spreading effect of preparations of streptococcic proteins observed in this study is shown to be due to the effect of a substance with the heat lability of an enzyme, rather than to vascular effects of inflammation, by comparison of the heat lability of the two solutions.

A possible explanation is offered for the data presented in a recent report of increased susceptibility of rheumatic subjects to hyaluronidase.

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22. Collis, W. R. F.; Sheldon, W., and Hill, N. G.: Cutaneous Reactions in Acute Rheumatism, Quart. J. Med. **1**:511-525 (Oct.) 1932.

23. Myers, W. K.; Keefer, C. S., and Oppel, T. W.: Skin Reactions to Nucleoprotein of Streptococcus Scarlatinae in Patients with Rheumatoid Arthritis and Rheumatic Fever, J. Clin. Investigation **12**:279-289 (March) 1933.

VITAMIN A ABSORPTION IN THE NEWBORN

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IN 1946 a paper was presented from this laboratory in which it was shown that vitamin A when administered in aqueous mediums is absorbed more readily than vitamin A administered in oil.[1] In the course of these investigations, it was observed that in normal infants the absorption of vitamin A, as measured by the vitamin A tolerance test, tends to be low. Moreover, a review of the literature [2] indicated that the percentage of fat in the stool is higher in young children than is normally observed in older children.

These observations suggested to us that a diminished rate of intestinal absorption of fats in general, and more specifically vitamin A in oil, exists in young children. This phenomenon should be even more pronounced in the newborn. For this reason, our studies, in which we compared the intestinal absorption of vitamin A in aqueous dispersion with that of the vitamin in oily mediums, were extended to newborn infants, their vitamin A absorption being compared with that of older children and of adults. A study of the fat content of the stool of newborn infants as compared with that of older children was also included.

From the Department of Biochemistry and Pediatrics, the Jewish Hospital of Brooklyn.

1. Sobel, A. E.; Gottfried, S. P., and Kramer, B.: A Comparison of Vitamin A Levels in Children Following the Oral and Intramuscular Administration of Vitamin A in Oily and Aqueous Media, read before the One Hundred and Tenth Meeting of the American Chemical Society, Sept. 11, 1946.

2. Holt, L. E.; Courtney, H. M., and Fales, H. C.: A Study of Fat Metabolism of Infants and Young Children, Am. J. Dis. Child. **17**:241 (April) 1919; Fat Metabolism of Infants and Young Children, ibid. **18**:107 (Aug.) 1919. Holt, L. E.; Tidwell, H. C.; Kirk, C. M.; Cross, D. M., and Neale, S.: Studies in Fat Metabolism: Fat Absorption in Normal Infants, J. Pediat. **6**:427 (April) 1935. Gordon, H. H., and McNamara, H.: Fat Excretion of Premature Infants: Effect on Fecal Fat of Decreasing Fat Intake, Am. J. Dis. Child. **62**:328 (Aug.) 1941. William, H. H.: Fat Excretion by Normal Children, J. Nutrition **25**:379 (April) 1943. Harrison, G. A., and Sheldon, W. P. H.: Fæcal Fat Analyses in Children, Arch. Dis. Childhood **2**:338 (Dec.) 1927. Wang, C. C.; Hogden, C., and Genther, I.: Metabolic Study of Five Children with Nephrotic Syndrome: Fat and Protein Metabolism and Creatinine and Creatine Output, Am. J. Dis. Child. **58**:29 (July) 1939. Andersen, D. H.: Celiac Syndrome, ibid. **69**:141 (March) 1947.

TABLE 1.—*Comparison of Serum Vitamin A Levels of Normal Newborn Children and Normal Older Children After Administration of Fish Liver Oil**

Case Number	Age	Vitamin A Expressed in Micrograms/100 Cc. Serum † Fasting	3‡	6‡	9‡	12‡	24‡	Maximum Rise
		Newborn Children						
1	Newborn	36	23	84	76	88	57	52
2	Newborn	38	28	39	48	22	47	10
3	Newborn	12	18	14	21	17	12	9
4	Newborn	12	16	39	18	25	27	27
5	Newborn	18	72	45	49	31	30	54
6	Newborn	46	91	87	45	47	24	45
7	Newborn	5	19	17	14	15	9	14
8	Newborn	24	24	14	8	10	9	0
9	Newborn	14	14	12	22	13	10	8
10	Newborn	17	16	8	9	8	11	0
11	Newborn	28	40	..	38	30	17	12
12	Newborn	31	27	32	35	37	31	6
13	Newborn	13	12	14	16	19	15	6
Mean	.....	23	31	34	31	28	23	18
14	Newborn	24	19	90	86	137	..	113
15	Newborn	14	14	12	24	29	..	15
16	Newborn	43	46	39	42	36	..	3
17	Newborn	25	24	25	19	15	..	0
Mean	.....	24	30	36	34	34	..	22
18	Newborn	33	23	58	59	..	24	26
19	Newborn	13	17	126	70	..	26	113
20	Newborn	5	31	53	202	..	16	197
21	Newborn	31	44	49	71	..	42	40
Mean	.....	23	29	42	46	..	24	36
22	Newborn	31	31	27	29	..	..	0
23	Newborn	42	47	51	44	..	..	9
Over-all mean	.....	24	30	42	45	..	24	33
		Children from 3 Months to 12 Years of Age						
40	3 mo.	41	84	80	31	..	..	43
41	4 mo.	21	56	32	32	..	..	35
42	14 mo.	31	158	84	60	..	..	127
43	15 mo.	32	100	191	104	..	..	159
44	1½ yr.	27	299	192	91	..	..	272
45	2 yr.	27	284	144	108	..	..	257
46	2½ yr.	28	242	128	...	..	..	214
47	3 yr.	39	325	243	147	..	..	286
48	3 yr.	48	281	229	192	..	..	233
49	3½ yr.	40	400	225	151	..	..	360
50	5 yr.	45	59	119	156	..	..	111
51	8 yr.	33	394	111	96	..	..	361
52	8 yr.	50	389	486	168	..	..	436
53	8 yr.	28	658	324	173	..	..	630
54	9 yr.	44	268	215	150	..	..	224
55	12 yr.	51	81	278	161	..	..	227
Mean	14 mo. to 12 yr. (cases 42-55)	37	281	212	134	..	..	278

* Oil 1 is percomorph liver oil.
† One microgram of vitamin A is equivalent to 3.57 U. S. P. units.
‡ Hours after test dose of 6,000 U. S. P. units per pound (13,500 units per kilogram) of body weight.

Vitamin A tolerance tests were performed by administering 6,000 U. S. P. units of vitimin A per pound of body weight in the form of oil 1.[3] For comparison, vitamin A tolerance tests were performed on older children who were given oil 1 in orange juice. The mixture was prepared immediately before use, in order to eliminate any effect dilution with orange juice might have on the stability of vitamin A. In some cases the oil was given directly.

TABLE 2.—*Fecal Fat Content of Newborn Children as Compared with That of Older Children*

Fecal Fat Content in Newborn Children							
Case No.	Fat in Dried Feces, %	Case No.	Fat in Dried Feces, %	Case No.	Fat in Dried Feces, %	Case No.	Fat in Dried Feces, %
16	26.0	25	41.1	31	50.7	4	56.1
22	27.2	37	42.3	20	51.2	126	56.8
23	28.8	15	42.6	127	51.4	17	57.2
21	34.4	8	43.6	24	51.4	120	60.0
121	36.3	32	44.0	124	51.6	128	60.4
125	37.2	122	44.3	5	51.9	18	61.2
24	37.5	19	44.4	13	52.0	123	61.8
11	38.0	28	45.2	29	52.4	...	....
7	38.4	38	47.3	27	54.0	...	....
12	39.8	9	48.2	10	54.3	...	....
26	40.4	30	50.5	6	55.4	...	....
Average					46.2		
Standard deviation					9.25		

Fecal Fat Content of Older Children (1-12 Years)		
Case No.	Age, Years	Fat in Dried Feces, %
129	1	20.6
130	2½	28.8
131	3	20.8
132	3½	10.6
133	4½	22.2
134	8	6.4
135	9	11.2
136	9½	14.2
137	12	13.8
Average	16.5	
Standard deviation	7.05	

To newborn children vitamin A was given before the morning feeding by means of a stomach tube. The infants' routine was not interrupted otherwise. To the older children vitamin A was given before breakfast. No other vitamin A supplement was given to either group during the test period. The results are given in table 1 and the mean values in chart 1

It may readily be observed that there exists a striking diminution in the absorption of vitamin A dissolved in oil in newborn children, as measured by the vitamin A tolerance test, the average maximum rise

3. Oil 1 is percomorph liver oil containing 60,000 U. S. P. units of vitamin A per gram in the form of esters.

being 33 micrograms per hundred cubic centimeters of serum, as compared with the average maximum rise of 278 micrograms per hundred cubic centimeters of serum in children from 1 to 12 years of age.

The values for fecal fat shown in table 2 tend to substantiate these findings. In the newborn infants, the values for fecal fat were from 26 to 62 per cent of dried stool, with a mean value of 46.2 per cent and a standard deviation of 9.25. In contrast, the values for fecal fat of the older children were from 6 to 29 per cent, with a mean value of 16.5 per cent and a standard deviation of 7.05.

We made an investigation to determine whether the newborn infant will show a greater absorption of vitamin A in an aqueous dispersion, similar to that found for the normal older child and for the child with the celiac syndrome.[4] A group of newborn infants were given a vitamin A preparation, previously referred to as aqueous dispersion I[5]

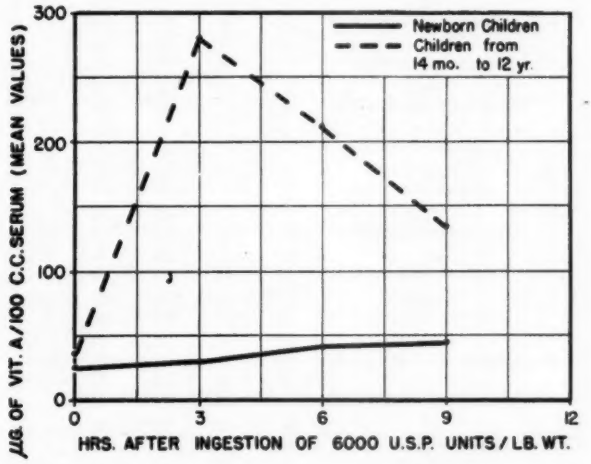


Chart 1.—Comparison of vitamin A tolerances of newborn children with that of older children to oil 1.

4. (*a*) Sobel, Gottfried and Kramer.[1] (*b*) Kramer, B.; Sobel, A. E., and Gottfried, S. P.: Serum Levels of Vitamin A in Children, Am. J. Dis. Child. **73**:543 (May) 1947.

5. (*a*) Sobel, Gottfried and Kramer.[1] (*b*) Kramer, Sobel and Gottfried.[4b] (*c*) Sobel, A. E.; Sherman, M.; Lichtblau, J.; Snow, S. D., and Kramer, B.: Comparison of Vitamin A Liver Storage Following Administration of Vitamin A in Oily and Aqueous Media, J. Nutrition **35**:225-238 (Feb.) 1948. (*d*) The preparation is called vifort.® The source of vitamin A was the nonsaponifiable fraction of fish liver oil. Each 0.6 cc. contained 5,000 U. S. P. units of vitamin A, 1,200 U. S. P. units of vitamin D, 1.8 mg. of thiamine hydrochloride, 0.6 mg. of riboflavin, 0.3 mg. of pyridoxine hydrochloride, 60 mg. of ascorbic acid, 3 mg. of nicotinamide, 1.2 mg. of calcium pantothenate and 132 mg. of extract of rice polishings, as well as choline, inositol and biotin vitamers and 16 per cent of polyoxyethylene sorbitan monolaurate, which is the dispersing agent.

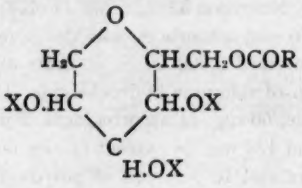
except that 16 per cent of the dispersing agent [6] was used instead of the 11 per cent previously employed.[4] All but 3 of the children were

TABLE 3.—*Comparison of Serum Vitamin A Levels in Normal Newborn Children Using Oil 1 or Oil 2* and Aqueous Dispersion I* [5d]

		Vitamin A Expressed in Micrograms/100 Cc. Serum						
Case No.	Preparation	Fasting	3†	6†	9†	12†	24†	Maximum Rise
1	Oil 1	36	23	84	76	88	57	52
	Aqueous dispersion I	57	444	296	48	..	..	387
2	Oil 1	38	28	39	48	22	47	10
	Aqueous dispersion I	47	142	108	116	..	..	95
4	Oil 1	12	16	39	18	25	27	27
	Aqueous dispersion I	27	136	126	97	..	..	109
5	Oil 1	18	77	45	49	31	29	59
	Aqueous dispersion I	29	258	210	160	..	..	229
6	Oil 1	46	88	87	45	47	24	42
	Aqueous dispersion I	24	215	201	101	..	..	191
16	Oil 1	43	46	39	43	36	43	3
	Aqueous dispersion I§	11	248	249	156	..	..	238
18	Oil 1	33	14	58	59	..	24	26
	Aqueous dispersion I	24	94	57	53	..	24	70
19	Oil 1	13	17	126	70	..	26	113
	Aqueous dispersion I	26	100	75	82	..	..	74
20	Oil 1	5	31	53	202	..	16	197
	Aqueous dispersion I	16	147	111	90	..	..	131
21	Oil 1	31	44	49	71	..	31	40
	Aqueous dispersion I§	42	207	105	74	..	..	165
22	Oil 1	31	31	27	29	..	60	0
	Aqueous dispersion I	60	147	102	76	..	..	87
Mean	Oil 1	28	37	59	65	42	37	52
	Aqueous dispersion I	33	194	149	96	..	..	161
24	Oil 2	6	20	118	154	161	75	155
	Aqueous dispersion I‡	75	434	447	340	..	..	372
25	Oil 2	14	65	43	14	..	14	51
	Aqueous dispersion I	4	277	146	81	..	..	273
26	Oil 2	21	26	20	11	..	21	5
	Aqueous dispersion I§	..	275	174	53	..	..	..
Mean	Oil 2	14	37	60	60	..	36	70
	Aqueous dispersion I	40	329	256	158	..	..	323
Over-all mean	Oil 1 and 2	25	37	59	64	59	35	56
	Aqueous dispersion I	34	223	172	109	..	..	186

* In 11 cases oil 1 (vitamin a ester) and in 3 cases oil 2 (vitamin A alcohol) were given. One microgram of vitamin A is equivalent to 3.57 U. S. P. units. (See footnotes 3 and 7.)
† Hours after test dose of 6,000 U. S. P. units per pound of body weight.
‡ Aqueous dispersion I was given in the feeding formula.
§ Aqueous dispersion I was given on the first day and oil 1 or oil 2 on the second day of testing.

6. The dispersing agent used was polyoxyethylene sorbitan monolaurate. This compound is an edible dispersing agent. Its structural formula is:



where R represents the lauryl radical, and X, the polyoxyethylene groups (total approximately 20).

given oil 1;[8] these 3 infants were given oil 2[7] on the first day and aqueous dispersion I on the following day. Occasionally, the aqueous solution was given on the first day and the oil on the next day, in order to eliminate any factor that might arise due to the massive dose of vitamin A supplied on the first day of testing. The results given in table 3 and chart 2 show notable improvement in absorption with aqueous dispersion I as compared with the absorptions with oil 1 and oil 2. The mean maximum rise with aqueous dispersion I was 186 micrograms per hundred cubic centimeters of serum, as compared with a mean maximum rise of 56 micrograms per hundred cubic centimeters of serum with the same amount of vitamin A in oil. The maximum rise not only was higher with vitamin A dispersed in aqueous medium but took place earlier. The average rise three hours after the administration

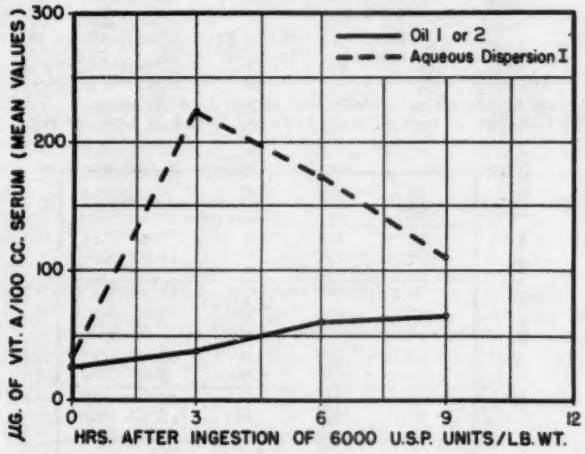


Chart 2.—Comparison of vitamin A tolerances of newborn infants when using oil 1[8] or oil 2[7] and those of infants when using aqueous dispersion I.[5d]

of the test dose was 37 micrograms per hundred cubic centimeters of serum with oil, as compared with 223 micrograms per hundred cubic centimeters of serum with aqueous dispersion I. Although there was no significant difference dependent on which product was given first, the twenty-four hour level, which was the fasting level on the second day of testing, was higher in general than the initial fasting level.

Embree[8] has recently suggested that in our previous studies[1] the improved absorption of vitamin A with aqueous dispersion I may have

7. In oil 2 the vitamin A is contained as the alcohol. A nonsaponifiable fraction of fish liver oil, containing 800,000 to 1,000,000 U. S. P. units of vitamin A per gram, was diluted with maize oil to the strength of oil 1, which contains 60,000 U. S. P. units per gram.

8. Embree, N. D.: Fat Soluble Vitamins, in Luck, J. M., and Smith, J. H. C.: Annual Review of Biochemistry, 1940-1945, Stanford University, Calif., Stanford University Press, 1947, vol. 16, pp. 323 and 335-336.

TABLE 4.—*Comparison of Serum Vitamin A Levels in Normal Newborn Infants When Receiving Vitamin A Ester (Oil 1) and When Receiving Vitamin A Alcohol in Maize Oil (Oil 2)*

		Vitamin A Expressed in Micrograms/100 Cc. Serum *						
Case No.	Vitamin A	Fasting	3†	6†	9†	12†	24†	Maximum Rise
7	Ester	5	19	17	14	15	9	14
	Alcohol	9	22	21	22	..	..	13
8	Ester	24	24	14	8	10	9	0
	Alcohol	9	30	29	..	..	..	21
9	Ester	13	14	12	22	13	11	9
	Alcohol	11	7	10	21	16	..	10
10	Ester	17	16	8	9	8	11	0
	Alcohol	11	11	8	16	19	..	7
11	Ester	28	40	23	38	30	17	12
	Alcohol	17	15	18	29	..	..	12
12	Ester	31	27	32	35	37	31	6
	Alcohol	31	34	35	28	40	..	9
13	Ester	13	12	14	16	19	15	6
	Alcohol	15	14	17	22	17	..	7
Mean	Ester	19	22	17	20	19	15	7
	Alcohol	15	19	20	23	23	..	11

* One microgram of vitamin A is equivalent to 3.57 U. S. P. units.
† Hours after test dose of 6,000 U. S. P. units per pound of body weight.

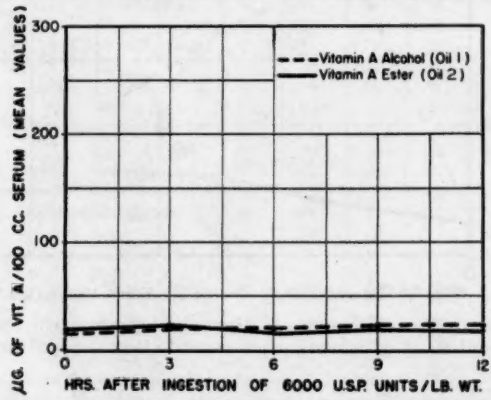


Chart 3.—Comparison of vitamin A tolerances in newborn infants when using vitamin A ester (oil 1) and those of infants when using vitamin A alcohol in maize oil (oil 2).

been due to the fact that in aqueous dispersion vitamin A is present as the free alcohol and in oil 1 as the ester. To determine whether some of the improvement with the aqueous dispersion is due to the fact that vitamin A is present as the alcohol, vitamin A tolerance tests were performed on the newborn child in which oil 1, containing vitamin A as ester, was compared with oil 2, in which vitamin A was present as the alcohol. The results are given in table 4 and chart 3. There were no significant differences in the absorption of vitamin A between the vitamin A alcohol in oil and the vitamin A ester in oil. That the improved absorption with aqueous mediums was not due directly to

the dispersing agent per se has been shown previously.[4] Thus, it may be stated with fair assurance that improved absorption with aqueous dispersion I is due to the medium, and not to the form, in which vitamin A is present.

TABLE 5.—*Comparison of Serum Vitamin A Levels in Normal Newborn Children When Receiving Aqueous Dispersion I and When Receiving Aqueous Dispersion II*

Case. No.	Preparation	Vitamin A Expressed in Micrograms/100 Cc. Serum * Fasting	3†	6†	9†	24†	Maximum Rise
Aqueous Dispersion I Administered on First Day of Testing							
27	Aqueous I	28	440	265	72	28	414
	Aqueous II	28	508	371	173	..	480
28	Aqueous I	10	263	363	92	34	353
	Aqueous II	34	408	249	178	..	374
29	Aqueous I	6	210	420	187	35	414
	Aqueous II	35	345	612	614	..	579
30	Aqueous I	5	188	137	129	48	183
	Aqueous II	48	169	227	230	..	182
31	Aqueous I	11	160	365	76	58	354
	Aqueous II	58	222	161	134	..	164
32	Aqueous I	6	167	104	84	31	161
	Aqueous II	31	237	198	188	..	206
33	Aqueous I	10	168	130	58	15	158
	Aqueous II	15	248	155	92	..	233
Mean	Aqueous I	11	228	255	99	36	291
	Aqueous II	36	307	282	230	..	317
Aqueous Dispersion II Administered on First Day of Testing							
34	Aqueous II	11	409	178	93	35	398
	Aqueous I	35	232	228	207	..	197
35	Aqueous II	24	294	149	79	35	260
	Aqueous I	35	840	351	107	..	805
36	Aqueous II	7	216	280	78	44	273
	Aqueous I	44	344	434	198	..	390
37	Aqueous II	17	211	121	76	44	194
	Aqueous I	44	205	210	84	..	166
38	Aqueous II	10	380	278	226	30	370
	Aqueous I	30	569	328	250	..	539
39	Aqueous II	23	246	118	71	41	223
	Aqueous I	41	250	182	72	..	208
Mean	Aqueous II	17	296	187	104	38	286
	Aqueous I	38	407	289	152	..	384
Over-all mean..	Aqueous II	23	310	270	124	36	333
	Aqueous I	27	299	238	171	38	303

* One microgram of vitamin A is equivalent to 3.57 U. S. P. units.
† Hours after test dose of 6,000 U. S. P. units per pound of body weight.

In our earlier reports,[4] aqueous dispersions containing the same concentrations of vitamin A but different concentrations of the dispersing agent were compared. Aqueous dispersion I contained, in addition to vitamin A, 11 per cent of the dispersing agent and other vitamin supplements. Aqueous dispersion II contained the same amount of vitamin A, but 20 per cent of the dispersing agent and no supplements. Dispersion II gave better absorption than dispersion I, as measured

by the vitamin A tolerance test. The question arose whether the vitamin supplement had any effect.

For this reason, aqueous dispersions I and II similar to those previously described [4] were prepared, except that both contained 16 per cent of the dispersing agent instead of the original 11 per cent in dispersion I and the 20 per cent in dispersion II.

A series of studies were made in which the vitamin A tolerance of newborn infants given aqueous dispersion I was compared with the tolerance of infants given aqueous dispersion II. The results are given in table 5 and chart 4. The mean maximum rise of aqueous dispersion I was 291 micrograms per hundred cubic centimeters of serum, and the mean maximum rise of aqueous dispersion II was 317 micro-

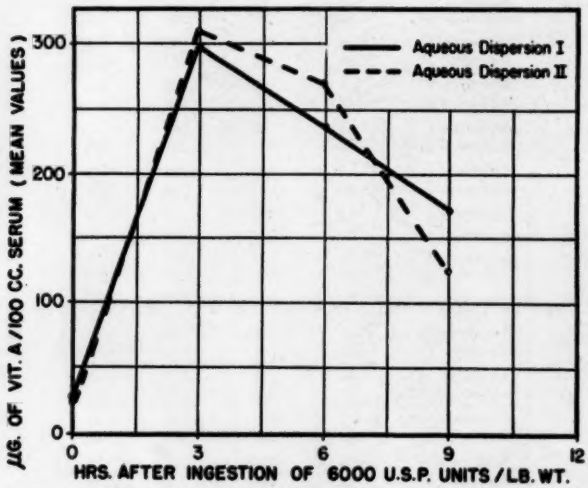


Chart 4.—Comparison of vitamin A tolerances in newborn infants when receiving aqueous dispersion I and when receiving aqueous dispersion II.

grams per hundred cubic centimeters of serum. It appeared that the maximum rise showed no significant differences; however, in many cases the maximum rise took place earlier with aqueous dispersion II and produced a higher level after nine hours than that with aqueous dispersion I. This result indicated either that aqueous dispersion I had a different behavior or that saturation with vitamin A was produced by the test on the preceding day, slowing up the absorption on the second day. It is of interest to note that the fasting level on the second day, which was also the 24 hour level of the first test, was higher than the inital fasting level. To evaluate these points, the order of administration was reversed by giving aqueous dispersion II the first day and aqueous dispersion I the second day of testing. The mean maximum rise of aqueous dispersion I was 384 micrograms per hundred

cubic centimeters of serum, and that of aqueous dispersion II, 286 micrograms per hundred cubic centimeters of serum, the higher maximum rise taking place this time with aqueous dispersion I, which was given on the second day of testing. Again, the nine hour value was higher on the second day of testing than on the first day. In some cases the difference was not so marked as in the first series. Thus it seems that saturation with aqueous dispersions I or II on the first day had a mild, but definite, influence on vitamin A tolerance on the second day of testing with an aqueous dispersion. There was no essential difference between the vitamin A absorption obtained with aqueous dispersion I and that with aqueous dispersion II. The conclusion may be drawn that the supplements present in aqueous dispersion I [4b] are not a significant factor in vitamin A absorption, but all evidence points to the importance of the concentration of dispersing agent present.

TABLE 6.—*Comparison of Serum Vitamin A Levels in 4 Normal Adults When Using Oil 1 and When Using Aqueous Dispersion I*

		Vitamin A Expressed in Micrograms/100 Cc. Serum *				
Case No.	Preparation	Fasting	3†	6†	8†	Maximum Rise
100	Oil 1	42	286	71	71	244
	Aqueous I	50	518	142	100	459
101	Oil 1	24	42	83	89	65
	Aqueous I	39	690	133	89	651
102	Oil 1	37	73	132	78	95
	Aqueous I	49	425	160	85	376
103	Oil 1	25	46	385	190	360
	Aqueous I	38	672	387	120	634
Mean	Oil 1	32	112	168	107	191
	Aqueous I	46	576	206	101	530

* One microgram of vitamin A is equivalent to 3.57 U. S. P. units.
† Hours after test dose of 1,000 U. S. P. units per pound of body weight.

The data so far presented establish as fact the observation that an aqueous dispersion of vitamin A is much more readily absorbed than is vitamin A in oil, both in newborn children and in children of the older age group.[4] The question arose whether adults would react in the same way. We investigated this problem by performing vitamin A tolerance tests on 4 normal young adults. Aqueous dispersion I was compared with oil 1, the test dose being 1,000 U. S. P. units per pound (2,200 units per kilogram) of body weight. The results are given in table 6 and chart 5. The mean maximum rise with aqueous dispersion I was 530 micrograms per hundred cubic centimeters of serum, and the mean maximum rise due to oil 1 was 191 micrograms per hundred cubic centimeters of serum. As may be readily observed, the results are similar to those obtained in newborn infants and in older children.

Since the completion of these investigations, Lewis and associates[9] reported increased absorption of vitamin A from aqueous solutions containing solubilizers different from ours, and Popper, Steigmann and Dyniewicz,[10] in a study of hepatic disease, reported increased absorption of vitamin A with aqueous preparations similar to ours.

COMMENT

It is evident from the data presented (tables 1 and 4; charts 1 and 3) that there is impairment of absorption of vitamin A from oily mediums in the newborn child, as compared with that in the older child when measured by the vitamin A tolerance test. Indirect evidence that the mechanism of fat absorption in the newborn child is not fully developed

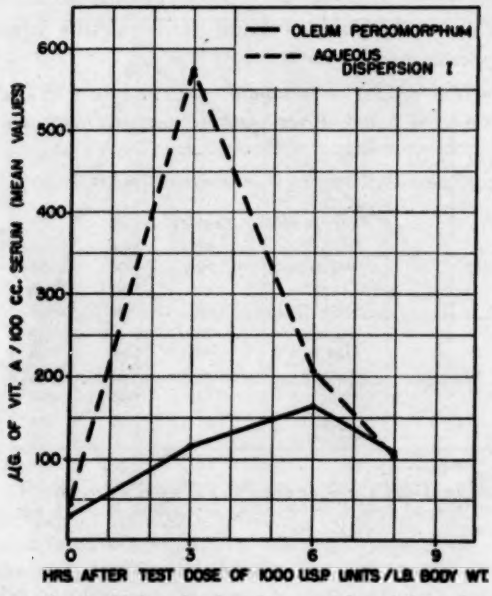


Chart 5.—Comparison of vitamin A tolerances in adults when receiving oil 1[8] and when receiving aqueous dispersion I.[5d]

is shown by the high percentage of fecal fat reported in the literature[2] and confirmed in our studies (table 2). An important finding which is in harmony with the concept of poor absorption of fat in newborn children was the observation that certain children, especially premature infants, respond to administration of vitamin D in oil only when it is given in huge doses.[11]

9. Lewis, J. M.: Bodansky, O.; Birmingham, J., and Cohlan, S. Q.: Comparative Absorption, Excretion, and Storage of Oily and Aqueous Preparations of Vitamin A, J. Pediat. **31**:496 (Nov.) 1947.

10. Popper, H.; Steigmann, F., and Dyniewicz, H. A.: Treatment of Endogenous Hypovitaminemia in Liver Disease, J. Lab. & Clin. Med. **32**:1403 (Nov.) 1947.

11. Kramer, B.: Vitamin D Therapy, J. Mt. Sinai Hosp. **8**:188 (Sept.-Oct.) 1941.

This impaired absorption apparently is not due to the absence of lipolytic enzymes in the intestine of the newborn child, although they are present in lower concentration than in the older child.[12] McCoord and associates[13] obtained approximately similar increases in serum vitamin after the administration of vitamin A alcohol and vitamin A ester in normal newborn children. However, in children with cystic fibrosis of the pancreas, in which pancreatic enzymes are practically absent, the vitamin A alcohol produced a much greater increase of vitamin A in the blood serum than did the vitamin A esters.

The poor absorption of fats, more specifically vitamin A in oil, in the newborn infant may be due to a factor in the intestinal wall. It is also possible, of course, that the mechanism for the transportation and storage of fats and fat-soluble substances is not so well developed in the newborn infant as in the older child. More exact studies on the structure of the intestine, the enzymes present and the mechanism of absorption and transportation of fat in the newborn are indicated.

As shown in table 3 and chart 2, in the newborn infant there is far better absorption of vitamin A in an aqueous medium than in an oily solution, as measured by the vitamin A tolerance test. In this connection it may be noted that in milk, which is the natural food of infants, fat-soluble vitamins are present in aqueous dispersion. Better absorption of fat-soluble vitamins from an aqueous dispersion may be the explanation of the finding that in children[14] "the definite curative action of as little as 40 Steenbock units daily shows vitamin D milk to be our most effective antirachitic agent."[15]

The question may be raised whether the increased blood levels obtained with the aqueous dispersion of vitamin A represent increased absorption or not. It was shown by Sobel and associates[5c] that storage of vitamin A in the liver of normal young rats was three times as great with aqueous dispersions I and II as with the same amount of vitamin A in oil 1 and oil 2. Halpern, Biely and Hardy[16] showed that the bioassay value of vitamin A, as measured by the growth of

12. Smith, C. A.: The Physiology of the Newborn Infant, Springfield, Ill., Charles C Thomas, Publisher, 1945, pp. 173-183.

13. McCoord, A. B.; Katsampes, C. P.; Lavender, C. F.; Martin, F. T.; Ulstrom, R. A; Tully, R. H., and Keenan, A. T.: The Absorption of Oily and Aqueous Preparations of Ester and Alcohol Vitamin A by Normal Children and Children with Various Diseases, Pediatrics **2**:652 (Dec.) 1948.

14. Kramer, B., and Gittleman, I. F.: Vitamin D Milk in the Treatment of Infantile Rickets, New England J. Med. **209**:906 (Nov. 2) 1933.

15. The source of vitamin D fed the children was either from cows fed irradiated yeast or cow's milk fortified with vitamin D by ultraviolet irradiation. At present, milk as a rule is fortified with vitamin D from outside sources.

16. Halpern, G. R.; Biely, J., and Hardy, F.: Utilization of Vitamin A in Water Emulsion, Science **106**:40 (July 11) 1947.

chicks, was higher with vitamin A in aqueous medium than with vitamin A in oil. In view of these findings, one can state with fair assurance that the sharp rise in the vitamin A tolerance curve obtained with the aqueous dispersions, as contrasted with the relatively flat curves obtained with oily solutions, actually represents improved absorption and retention of vitamin A, rather than merely a temporary high blood level.

The present experiments show that, in addition to the factors mentioned by Clausen [17] as affectig the ability of the intestine to absorb vitamin A, the medium must be considered. The probable explanation is that the size of the individual vitamin A–containing particles is in itself a factor in absorption. The importance of particle size was indicated by Frazer and associates.[18] They postulated two methods of absorption for triglycerides—one involving hydrolysis as a preliminary step, and the other, simple reduction to a particle size of 0.5 micron or less.[19] The evidence presented would indicate that in general the particle size is a more effective factor than the one involving preliminary hydrolysis. They showed that olive oil in the intestine of the rat is dispersed to a fine particle size of less than 0.5 micron. Furthermore, in rats fed paraffin in an aqueous dispersion containing particles of an average size of less than 0.5 micron, absorption by the intestine was equal to that observed with olive oil dispersed in an equal particle size in water. Paraffin itself is not absorbed at all by the intestine. Lundbaek and Maaløe,[20] however, were unable to repeat the paraffin experiments. It is also possible that, in addition to its effect in reducing particle size, the dispersing agent itself may play a part in improved absorption, by acting as a wetting agent, by changing the interfacial tension or by changing the nature of the surface of the intestine or the channels through which the vitamin A is absorbed.

Clausen [17] has shown the pathway of vitamin A when administered in oil. This consists of hydrolysis prior to absorption and reesterification in the wall of the small intestine. Most of the esters pass by way of the lymphatics through the thoracic duct into the blood stream. By this and by future studies, we hope to determine whether the pathway of absorption of vitamin A is the same with aqueous dispersion as that with oils.

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17. Clausen, S. W.: Absorption of Vitamin A and Its Storage in Tissues, in Harvey Lectures, 1942-1943, Baltimore, Williams & Wilkins Company, 1943, p.199.

18. Frazer, A. C.; Schulman, S. H., and Stewart, H. C.: Emulsification of Fat in the Intestine of the Rat and Its Relation to Absorption, J. Physiol. **103**:306 (Dec. 15) 1944.

19. Frazer, A. C.: The Absorption of Fat from the Intestine, Chem. & Indust. **27**:379 (July 5) 1947.

20. Lundbaek, K., and Maaløe, O.: Nonabsorption of Finely Emulsified Paraffinum Liquidum in the Intestine of the Rat, Acta physiol. Scandinav. **13**:247, 1947.

It has recently been suggested by Embree [8] that the improved absorption with aqueous dispersion I that we obtained in our previous studies [4] may have been due to the fact that vitamin A is present in the aqueous solution as the free alcohol and in oil 1 as the ester. This postulate is not borne out by our experiments. The vitamin A tolerances with oil 1 (vitamin A ester) and with oil 2 (vitamin A alcohol) were similar, both indicating diminished absorption in the newborn as compared with absorption in the older child. Moreover, rats fed oil 1 and rats fed oil 2 had identical stores of vitamin A [5c] in the liver.

The supplements in aqueous dispersion I did not result in lowered vitamin A absorption, as might have been expected from work reported earlier.[4] In the earlier work, however, the percentage of the dispersing agent present in dispersion I was 11 per cent and that in dispersion II 20 per cent, whereas in the experiments reported in this paper the percentages of dispersing agent present are the same for the two dispersions, i. e., 16 per cent. It seems that the percentage of dispersing agent is an important factor in determining the magnitude of improvement in absorption. This may be due to the particle size or to interfacial tension or to a combination of the two. More systematic studies are being undertaken to elucidate this point.

That vitamin supplements may have beneficial effects on the body economy was pointed out by the work of Dye, Porter and Kelly,[21] in which they indicated that in rats vitamin A and vitamin B may have a synergistic effect, since the two together were more effective in reducing the number of foci of keratinized epithelial cells than vitamin A alone.

It is worthy of note that the experiments reported in this paper indicate that there is better absorption in adults, as well as in newborn infants, from an aqueous dispersion of vitamin A than from vitamin A in oil. The same phenomenon was observed in older children, as previously reported.[4] Thus it is likely that the standard requirements for vitamin A when the vitamin is given in aqueous dispersion will ultimately be revised to a lower level than is advised at present. Such lowered requirements will probably apply also to such other fat-soluble vitamins as D, E and K, to essential fatty acids and to fats when given in aqueous dispersions.

METHODS

The method employed for the estimation of vitamin A was that described by Bessey and his colleagues,[22] with some modifications. The changes consisted in (1) a different method of collecting the blood and (2) the use of quartz tubes in

21. Dye, M.; Porter, T., and Kelly, E.: The Conjoint Effects of Varied Intakes of Thiamine and Vitamin A on Rats, J. Nutrition **33**:459 (April) 1947.

22. Bessey, O. A.; Lowry, O.; Brock, M. J., and Lopez, J. A.: The Determination of Vitamin A and Carotene in Small Quantities of Blood Serum, J. Biol. Chem. **166**:177 (Nov.) 1946.

place of glass tubes for irradiation. This was found necessary, since incomplete destruction of vitamin A was obtained after irradiation in ordinary glass tubes.

The blood was taken from the heel of the infant. The blood collecting tube consisted of a 3 to 5 mm. diameter glass tube drawn to a capillary 0.5 to 1.0 mm. in diameter. The length of the wider end was 5 to 10 cm., and that of the drawn-out portion, from 4 to 8 cm. The walls of the tube were covered with a thin film of potassium oxalate. A piece of rubber tubing was connected to the wide end of the tube and the blood drawn up by the gentle suction of the mouth. The capillary tip of the tube was sealed with low melting sealing wax (pyseal®) and the wide tip stoppered with a tight-fitting rubber cap, and the tube was centrifuged. The plasma was drawn off and the vitamin A content determined from this point according to the method described by Bessey and associates [22] except that the irradiation of the extract was carried out in small quartz tubes. The amount of plasma used was from 0.03 to 0.06 cubic centimeter. No significant differences were found between vitamin A levels in the plasma and those in the serum.

The results were considered valid only if (1) complete destruction of a vitamin A standard in xylol-kerosene-mixture (1:1) was obtained after irradiation, as

TABLE 7.—*Effect of Hemolysis on Serum Vitamin A and Carotene Values* [24]

Degree of Hemolysis	Log Io/I 328 Microns		Vitamin A, Micrograms per 100 Cc. Serum	Carotene, Micrograms per 100 Cc. Serum
	Before Irradiation	After Irradiation		
None	0.168	0.068	44	179
Severe	0.315	0.200	67	220
None	0.134	0.045	52	98
Definite	0.166	0.075	58	102
Severe	0.645	0.515	76	200

checked by reading at 328 microns and (2) satisfactory recovery was obtained. Determination of recovery consisted in the analysis of two samples of the same serum, to one of which a known amount of vitamin A in the xylol-kerosene mixture was added. The blood serum of a normal person was analyzed with each set of determinations.

A frequent source of error in this method is the effect that hemolysis has on both the vitamin A and the carotene values. The black readings, i. e., the readings at 328 microns after irradiation, were higher than those with unhemolyzed serum, increasing with the degree of hemolysis, and the carotene values show considerable increase, depending on the degree of hemolysis. Table 7 indicates differences due to various degrees of hemolysis. The method used, provided there exists only slight hemolysis, compares well with the Carr-Price method [4b] and the method of Sobel and Snow.[23]

Total values for fecal fat were determined on twenty-four hour specimens. The method used was a modification [24] of that described by Tidwell and Holt.[25]

23. Sobel, A. E., and Snow, S. D.: The Estimation of Serum Vitamin A with Activated Glycerol Dichlorohydrin, J. Biol. Chem. **171**:617 (Dec.) 1947.

24. Zymaris, M.; Natelson, S. R., and Zuckerman, J.: Personal communications to the authors.

25. Tidwell, H. C., and Holt, L. E.: Estimation of Total Lipids and Lipid Partition in Feces, J. Biol. Chem. **112**:605 (Jan.) 1936.

SUMMARY

Newborn children show diminished intestinal absorption of fats, more specifically vitamin A in oil, as compared with children above 1 year of age or with adults, as indicated by low vitamin absorption curves after administration of oleum percomorphum (vitamin A ester) or the nonsaponifiable fraction of fish liver oil (vitamin A alcohol) dissolved in maize oil. Values for fecal fat in infants are much higher than those for older children. When an aqueous dispersion (I) of the nonsaponifiable fraction of fish liver oil (vitamin A alcohol, containing the vitamin B complex and vitamins C and D) was fed, higher vitamin A absorption curves were observed. When an aqueous dispersion (II) of vitamin A containing the same amount of dispersing agent (16 per cent polyoxyethylene sorbitan monolaurate) was administered but no other vitamins were given, a rise similar to that found with dispersion I was obtained. Thus, it appears that in newborn children there is a diminished absorption of vitamin A in oil, which may be remedied when the vitamin A is given in an aqueous dispersion. Moreover, the percentage of dispersing agent, and not the absence of vitamin supplements, is the important factor in determining the magnitude of improved absorption.

In older children and in adults there is also improved absorption with aqueous dispersions, as measured by vitamin A tolerance curves.

Dr. S. M. Gordon, of Endo Products, Inc., prepared and supplied the various aqueous dispersions of vitamin A used in this study. Mead Johnson & Company provided a generous supply of oleum percomorphum.*

The Jewish Hospital of Brooklyn.

IRREGULARITIES OF BREATHING IN THE NEWBORN PERIOD

PHILIP J. HOWARD, M.D.
AND
A. ROBERT BAUER, M.D.
DETROIT

THE BREATHING of newborn infants has been known to be somewhat irregular in rhythm, depth and rate. Kymographic records of breathing during fussing and crying are so irregular in both premature infants and newborn, full term infants as to furnish little information. Such records during sleep, although still grossly irregular, can be analyzed. The records of premature infants, as reported previously,[1] showed gross changes in rate, rhythm and base line at the end of respiration and of tidal air. The records of the newborn infants here reported on showed the same type of irregularity as those of the premature infants formerly reported on by us and as those of the newborn infants reported on by Deming and Washburn.[2] The effect of the administration of a mixture low in oxygen in producing irregularity and Cheyne-Stokes respiration was shown in 7 of 10 infants and in producing Cheyne-Stokes respiration alone in 1 of 10. The effect of a mixture high in oxygen in causing a regular rhythm and improved breathing was shown in all 10 infants. The stimulation of breathing on administration of carbon dioxide in a mixture high in oxygen was shown in all infants. The concomitant chest and abdominal excursions were studied and showed phase irregularity, the chest contracting at times in response to the diaphragmatic pull of inspiration, while at other times the chest and abdomen expanded together in inspiration.

Measurements were made of the rate of respiration, volume of tidal air and volume of air inspired per minute. Partially quantitative measurements were made of the chest and abdominal excursions with each

From the Department of Pediatrics, Henry Ford Hospital.

1. Wilson, J. L.; Long, S. B., and Howard, P. J.: Respiration of Premature Infants: Response to Variations in Oxygen and to Increased Carbon Dioxide in Inspired Air, Am. J. Dis. Child. **63**:1080 (June) 1942.

2. Deming, J., and Washburn, A. H.: Respiration in Infancy: I. A Method of Studying Rates, Volume and Character of Respiration with Preliminary Report of Results, Am. J. Dis. Child. **49**:108 (Jan.) 1935.

respiratory movement. Since it is well established that each of these phenomena is dependent on the relative levels of oxygen and carbon dioxide in the blood, as well as in the respired air, these studies were made while the infant was breathing room air (20 per cent oxygen, 80 per cent nitrogen and 0.05 per cent carbon dioxide), a mixture low in oxygen (12 to 14 per cent oxygen and 88 to 86 per cent nitrogen), a mixture high in oxygen (68 to 72 per cent oxygen and 32 to 28 per cent nitrogen) and a mixture with carbon dioxide (3.5 to 5 per cent carbon dioxide, 68 to 72 per cent oxygen and 22.5 to 28.5 per cent nitrogen). These concentrations were achieved by giving plain air, 12.5 per cent oxygen, 100 per cent oxygen, and 5 per cent carbon dioxide in 95 per cent oxygen, respectively.

APPARATUS AND MATERIAL

A body plethysmograph was used, constructed according to the specifications of Deming and Washburn,[2] the infant's head protruding through a snug-fitting sponge rubber collar. Two circular rubber tubes, consisting of sections of "thyroid" drains, were arranged around the chest at the nipple line and around the abdomen at the umbilicus. These were attached by a rubber tube to a recording tambour so that changes in air volume with respiration could be recorded. A record of the entire change in volume of the infant's body was made with a Krogh spirometer connected to a kymograph. Thus, simultaneous records were obtained of the tidal air, the chest excursion and the abdominal excursion. A cellophane® enclosure was placed around the infant's head so that the mixtures of gas could be easily administered. The concentrations of gas were approximate, many samples being taken for analysis; but no constant analysis was made. A recording pen was used which held within itself a small quantity of oil-ink. The weight of this pen plus the weight of the recording arm was sufficient to give a certain measurable momentum, so that at high speeds of respiration the identical motion of the pen actually indicated less air respired than at low speeds of respiration. This factor was evaluated in our calibration and was also noted by Murphy and Thorpe.[3] This was unexpected, as we anticipated that at high speeds the needle would lag behind and record only a part of the real air motion. Instead, the recording needle overshot and recorded more air than actually moved. The application of chest and abdominal recorders and the placing of the infant in the plethysmograph were always followed by a variable period of waiting for the infant to go to sleep. All records were taken just after a meal and while the infants were asleep, the only exceptions being attempts to estimate vital capacity. The latter were records of extreme inspirations in crying which happened from time to time while an infant was under observation.

The 10 babies ranged in age from 5 to 30 days. Their weights ranged from 5 pounds 4 ounces (2,381 Gm.) to 7 pounds 2 ounces (3,232 Gm.). All were healthy, newborn babies, free from infection or recognized congenital deformity.

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3. Murphy, D. P., and Thorpe, E. S.: Breathing Measurements on Normal Newborn Infants, J. Clin. Investigation **10**:545 (Aug.) 1931.

OBSERVATIONS IN AIR

The rate of respiration in air varied from 35 to 67 per minute. These rates were counted in each instance for a full minute. It was evident that the respiratory rate was not uniform, even in sleep. The depth of sleep varied a great deal. If an infant was having Cheyne-Stokes breathing, it usually signified deep, quiet sleep. In such an infant the rate had to be taken for at least a full minute to get a true estimate, because of periods of apnea. In many instances an infant who was fussy would suddenly fall asleep, giving us the impression that his rate was still stimulated by exercise even though he was asleep. Varying states

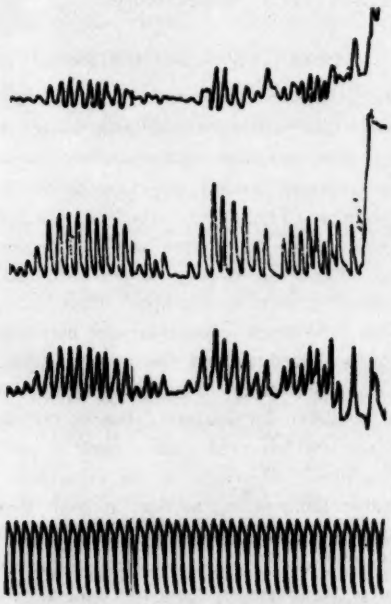

Fig. 1 (infant 5).—Breathing type 2, Cheyne-Stokes breathing in air on deep sleep. In all tracings the curves are as follows, from top to bottom. first, chest; second, abdomen; third, total air exchange, and lowest, time in seconds.

of digestion, muscle tone and circulation were at all times present, actually necessitating a different amount of oxygen. In general, the smaller infants had the higher rates.

The minute volume was carefully ascertained in each instance by measuring each inspiration, and the average tidal air was calculated from division of minute volume by rate. The minute volume in air varied from 413 to 1,040 cc., with an average of 731 cc. The minute volume indicates how much air is breathed by the different types of respiration. In general, the smallest and least well developed infants had the lowest minute volumes.

The minute volume per pound of body weight averaged 113 cc., with a range of 80 to 167 cc. This figure compares closely with other published figures, as shown in table 1.

TABLE 1.—*Comparison of Minute Volumes Reported by Various Authors*

Authors	Minute Volume, Cc.		Minute Volume in Cc. per Pound	
	Average	Range	Average	Range
Deming and Washburn [2]	1,078	354 to 2,007	131	59 to 230
Deming and Hanner [7]	851	225 to 1,835	127	38 to 248
Shaw and Hopkins [6]	600	698 to 795	...	120 to 300
Howard and Bauer	731	413 to 1,127	113	80 to 167

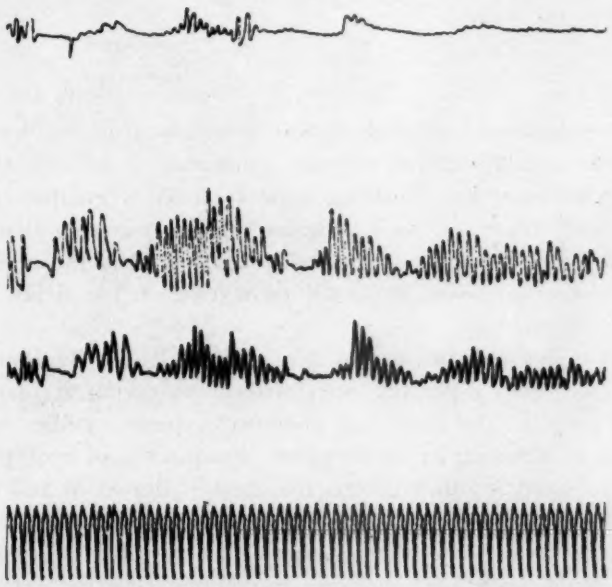

Fig. 2 (infant 6).—Breathing type 2, Cheyne-Stokes rhythm in air.

All 10 infants showed some degree of irregularity when breathing air, from a slight occasional short breath to Cheyne-Stokes breathing with irregularity. The types of irregularity shown here were previously reported by Deming and Washburn [2] and by Wilson, Long and Howard.[1] Only two of our records showed the cogwheel breathing described by Deming and Washburn,[2] and we attached no special significance to it. We classified respiratory irregularity in types as follows:

Breathing Type

1 Cheyne-Stokes rhythm with gross irregularity
2 Cheyne-Stokes rhythm with apnea
3 Periodic but with no apnea
4 Regular with occasional short breath (normal)
5 Stimulated, supernormal, regular and excessive, as seen with carbon dioxide stimulation

We called type 1 the least "efficient" and a sign of immature functioning of the respiratory mechanism. This classification is supported by lowest minute volumes in types 1 and 2 and highest minute volumes in type 5, with types 3 and 4 intermediate. Three examples of this are shown in tabular form:

Breathing Type	Minute Volume, Cc.	Atmosphere
Infant 2.—Age, 8 days		
1	401	Low oxygen
2	709	Air
4	853	High oxygen
5	2,089	Carbon dioxide and oxygen
Infant 3.—Age, 9 days		
1	365	Low oxygen
4	413	Air
4	495	High Oxygen
5	1,110	Carbon dioxide and oxygen
Infant 8.—Age, 21 days		
1	898	Low oxygen
2	1,040	Air
4	1,262	High oxygen
5	1,540	Carbon dioxide and oxygen

This classification, although it was generally true for 8 of the 10 infants, was notably untrue for the remaining 2 infants. In these, irregular Cheyne-Stokes breathing type 1 moved a greater volume of air and, therefore, was a more efficient type of breathing than regular type 4 for 1 infant and than Cheyne-Stokes type 2 in the other infant. This is another instance in which estimation of the depth of sleep would be contributory.

The phase of respiration was described at length by Bauer,[4] and, therefore, we were especially interested in observing it on these 10 infants. In adults, the chest and abdomen expand together with each inspiration, constituting a positive phase. Frequently, in weak premature infants, and often in other babies, the chest is drawn in and contracts as the abdomen expands with inspiration, constituting a negative phase. We observed in these newborn infants that the phase varied in each of them, being sometimes positive, sometimes negative. The simultaneous recording of chest, abdominal and plethysmographic tracings made this bizarre observation a little more understandable. In watching the movements of the recording pens, a fascinating sequence was seen. The spirometer pen always started its upward swing a little in advance of the upward swing of the pen recording abdominal movements, which would signify that there was some effective inspiration before the abdomen had expanded to the point where it activated the air in the rubber tube surrounding it. This in turn was followed by the upward swing of the pen recording chest movement, the sequence constituting what we termed a positive phase. At times, the upward swing of the chest pen was delayed more than just described and even made a slight

4. Bauer, A. R.: Respiration in Newborn Infants, Am. J. Dis. Child. **60**:1342 (Dec.) 1940.

downward stroke before going up. This we considered as a combination of positive and negative phase. At other times, the entire excursion of the chest pen was downward, the upstroke being merely a return to the "base line." This is shown clearly in figure 4, where the plateau representing the pause at the end of expiration is at the top of the curve instead of at the bottom. This indicated a completely negative phase.

The explanation of this sequence is on the basis of several factors. It is apparent that newborn infants get their greatest respiratory effort from the diaphragm, a fact which is also true in the so-called involuntary

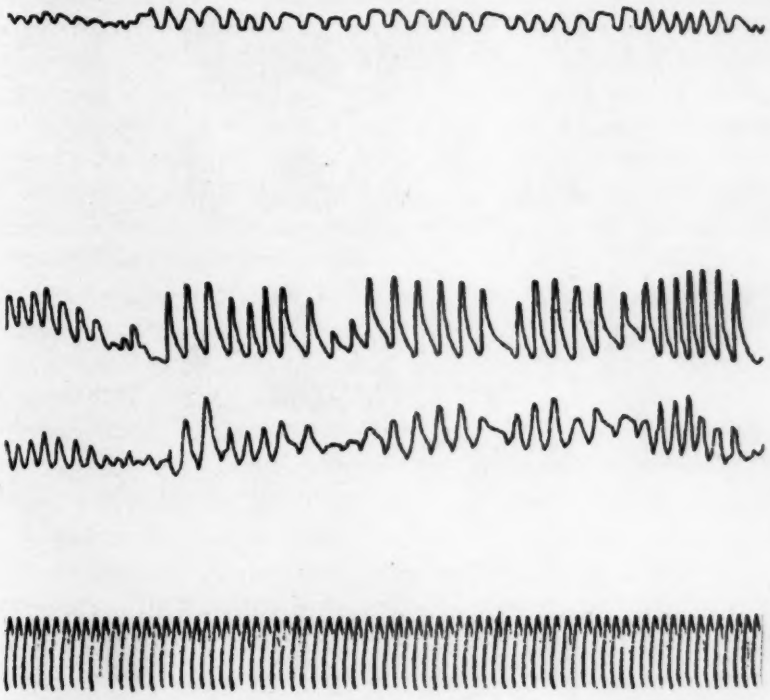

Fig. 3 (infant 3).—Breathing type 3, periodic rhythm without apnea, in air.

breathing of adults. The action of the chest is a secondary or accessory mechanism which is called into play when a more effective respiration is needed. The ability of the chest to perform this function is dependent on the angle of the ribs with the spine, the degree of solidarity of its bony and cartilaginous structures and the strength and functional development of the "accessory muscles of respiration." If the infant has reached a degree of maturity and vigor in which he is able to employ these accessory facilities effectively, his tendency will be more toward a positive phase, whereas, if he has not developed to this degree, he is more likely to be in a negative phase or at some point between the two.

The practical application of this information is open to some question. It is quite interesting to explain the mechanism of the respiratory movements, but we were not able to show that the positive phase was any more efficient than the negative phase so far as tidal air or minute volume are concerned. However, it must be remembered that this work was done on normal, healthy babies. The situation might be different in infants who are suffering respiratory embarrassment. In them, the ability to use their accessory facilities, or even effectively withstand the pull of the diaphragm, might be a matter of extreme importance.

Fig. 4 (infant 8).—Breathing type 1, irregular Cheyne-Stokes rhythm in low oxygen with a three second period of apnea. The phase is negative, with the abdomen contracted and the chest expanded. Gas analysis showed 11.75 per cent oxygen.

Or to state it another way: the inability of the infant to use his accessory facilities due to a chest so weak that it cannot withstand the pull of the diaphragm does not in itself contribute to respiratory difficulty, but, if the baby is in difficulty from some other reason, the ability to use a positive phase may prevent complete respiratory failure.

While fussing and crying, enough effort is made by the baby to produce a positive phase and enormously increase the tidal air. The largest recorded tidal air or single breath was 149 cc. Larger vital capacities

have been recorded by many observers [5] and depend somewhat on the weight of the baby, but mostly on the chance of recording an extreme inspiration. As Smith stated, "On certain points such as the vital capacity there is as yet no definite knowledge, nor indeed the likelihood of any . . ." All observations are presented in the tables.

OBSERVATIONS IN LOW OXYGEN ATMOSPHERE

The rate of respiration in an atmosphere low in oxygen, 12 to 14 per cent, was slightly less than in air, ranging from 24 to 70 per minute, with an average of 44.5. This was a lower rate than in air in 7 infants, an increase in 2 and an unchanged rate in 1 infant. The minute volume varied from 365 to 1138 cc., with an average of 791 cc. The 3 smallest infants again showed the lowest minute volumes. Four infants showed a decrease of minute volume compared with that in air; 3 showed a change of only 3 to 4 per cent, and 3 showed a significant increase of 33 to 111 per cent. Whether the low oxygen mixture was a depressant or stimulant depended on the maturity of the respiratory mechanism, and in these babies we have samples demonstrating that it was a stimulant, a neutral factor and a depressant.

The rhythm of breathing in the low oxygen mixture was of Cheyne-Stokes periodicity, with gross irregularity in 6 infants, classified as type 1. It was of Cheyne-Stokes character with measurable periods of apnea in 2 infants, classified as type 2, and of a normal rhythm in 2 infants, classified as type 4. Four infants changed from a normal rhythm in air to a Cheyne-Stokes rhythm in low oxygen. Two of these showed a decrease in minute volume of -11 and -3 per cent, while 2 showed an increase in minute volume of $+111$ and $+33$ per cent. Four infants had Cheyne-Stokes breathing in both air and low oxygen atmosphere. Of these 4 infants, 2 showed an increase in minute volume and 2 a decrease in minute volume. The 2 remaining infants showed regular normal rhythm in both air and the low oxygen mixture, 1 increasing and 1 decreasing the minute volume. We did not observe that Cheyne-Stokes breathing tended actually to produce a smaller minute volume, but rather we felt the infant with this type was always under a strain and that it was an indication of impending harm.

The phase of respiration was again indeterminate, not following any predictable pattern, some of the infants showing the positive phase and some the negative. There was no constant change in phase observed between air and the low oxygen mixture. All observations are presented in table form.

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5. Smith, C. A.: The Physiology of the Newborn Infant, Springfield, Ill., Charles C Thomas, Publisher, 1945.

TABLE 2.—*Measurements of Rate, Minute Volume and Tidal Air in Ten Normal, Newborn Infants*

				Air—20 per Cent Oxygen				Low—12.5 per Cent Oxygen				High—100 per Cent Oxygen				5 per Cent Carbon Dioxide and 95 per Cent Oxygen			
Infant No.	Age, Days	Weight Lb.	Weight Oz.	Rate per Minute	Minute Volume, Cc.	Average Tidal Air, Cc.	Rhythm* and Phase,† Type	Rate per Minute	Minute Volume, Cc.	Average Tidal Air, Cc.	Rhythm and Phase, Type	Rate per Minute	Minute Volume, Cc.	Average Tidal Air, Cc.	Rhythm and Phase, Type	Rate per Minute	Minute Volume, Cc.	Average Tidal Air, Cc.	Rhythm and Phase, Type
1	5	5	4	67	467.0	6.9	4	55	985.5	17.9	1	67	886.5	13.2	4	51	1,402.6	27.5	5
2	8	7	2	35	709.0	20.2	2	29	401.7	13.8	1	30	853.5	28.4	4	46	2,069.6	46.7	5
3	9	5	2	32	413.0	12.9	3 N	24	365.0	15.2	1 N	22	495.0	22.5	4 P	32	1,110.6	34.7	5 N
4	11	5	7	60	457.7	7.6	2 P	60	571.8	9.5	1 P	68	459.6	7.2	4 P	59	1,362.5	23.9	5 P
5	14	6	2	54	628.9	11.6	2 P	41	655.2	15.9	2 P	40	731.9	18.2	4 N	42	1,020.9	24.3	5 N
6	16	6	12	42	1,127.9	26.8	4 P	30	1,101.6	36.7	4 N	37	1,152.7	31.4	4 P	45	2,158.5	47.9	5 P
7	18	6	8	43	861.4	20.0	4 N	57	1,138.9	19.9	4 V	62	1,170.9	18.8	4 V	66	1,714.8	25.9	5 V
8	21	6	9	46	1,040.7	22.6	2 N	38	898.7	23.6	1 N	57	1,262.0	22.1	4 N	44	1,540.4	35.0	5 N
9	28	7	6	40	681.0	17.0	4	70	906.0	12.9	2	94	1,867.0	19.8	4	70	2,138.6	30.5	5
10	30	7	2	46	927.0	20.1	4 P	41	899.0	21.9	1 P	56	1,060.0	25.2	4 P	58	2,146.4	37.0	5 N
Average.....				46.5	731.3	16.5	....	44.5	792.3	18.7	....	53	993.9	20.7	....	51.3	1,666.0	33	....

* Breathing types are designated as follows: 1, Cheyne-Stokes with irregularity; 2, Cheyne-Stokes; 3, rhythmic without apnea; 4, regular, normal, and 5, supernormal, stimulated.

† P indicates positive phase, N, negative and V, partially negative phase.

OBSERVATIONS IN HIGH OXYGEN ATMOSPHERE

The rates in oxygen atmosphere of 68 to 72 per cent in the 10 infants varied from 22 to 94 per minute, with an average of 53. The rate increased as compared with the rate in air in 5 infants, remained the same in 1 infant and decreased in 4. The greatest increase was

TABLE 3.—*Rate per Minute, Minute Volume and Tidal Air, per Pound of Body Weight*

		Air—20 per Cent Oxygen			12.5 per Cent Oxygen			100 per Cent Oxygen			95 per Cent Oxygen and 5 per Cent Carbon Dioxide		
Age, Days	Weight, Lb.	Rate	Minute Volume, Cc.	Tidal Air, Cc.	Rate	Minute Volume, Cc.	Tidal Air, Cc.	Rate	Minute Volume, Cc.	Tidal Air, Cc.	Rate	Minute Volume, Cc.	Tidal Air, Cc.
5	5.25	12.76	88.95	1.3	10.4	187.7	3.4	12.7	168.7	2.5	9.7	267.1	5.23
8	7.125	4.9	99.05	2.8	4.0	56.3	1.9	4.2	119.7	3.9	6.4	290.2	6.5
9	5.125	6.2	80.58	2.5	4.6	71.1	3.0	4.3	96.5	4.4	6.2	216.5	6.8
11	5.4375	11.0	84.10	1.4	11.0	105.1	1.7	12.5	84.5	1.3	10.8	250.4	4.4
14	6.125	9.0	102.67	1.9	6.8	107.0	2.6	6.5	119.5	3.0	7.0	166.8	4.0
16	6.75	6.2	167.11	4.0	4.4	162.0	5.4	5.5	170.7	4.6	6.7	319.8	7.1
18	6.5	6.6	132.52	3.0	8.7	172.1	3.0	9.5	180.1	2.9	10.1	263.8	4.0
21	6.5625	6.9	158.58	3.4	5.7	136.1	3.6	8.6	191.2	3.3	6.7	233.3	5.3
28	7.375	5.4	92.33	2.3	9.5	122.4	1.7	12.7	252.3	2.7	9.5	287.6	4.1
30	7.125	6.5	130.10	2.8	5.8	125.2	3.1	7.9	149.3	3.5	8.2	302.3	5.2
rage.....			113.5	...	...	124.5	...	....	153.2	...	...	259.7	...

4.—*Rate, Minute Volume and Tidal Air Changes Showing per Cent Variation from Basic Value in Air When Other Oxygen Mixtures Were Given* *

				Air—20 per Cent Oxygen			12.5 per Cent Oxygen			100 per Cent Oxygen			95 per Cent Oxygen and 5 per Cent Carbon Dioxide		
nfant No.	Age, Days	Weight Lb.	Oz.	Rate	Minute Volume, Cc.	Tidal Air, Cc.	Rate	Minute Volume, Cc.	Tidal Air, Cc.	Rate	Minute Volume, Cc.	Tidal Air, Cc.	Rate	Minute Volume, Cc.	Tidal Air, Cc.
.....	16	6	12	42	1,127.9	26.8	— 28	— 2.3	+ 37	— 26	+ 13	+ 17	— 22	+ 62	+ 78.7
.....	9	5	2	32	413.0	12.9	— 25	— 11.0	+ 18	— 31	+ 20	+ 74	0	+168	+169
.....	14	6	2	54	628.9	11.6	— 21	+ 4.0	+ 37	— 26	+ 13	+ 56	— 22	+ 62	+109
.....	5	5	4	67	861.4	6.9	— 18	+111.0	+183	0	+ 90	+ 91	— 24	+200	+300
.....	21	6	9	46	1,040.7	22.6	— 17.4	— 13.6	+ 8.8	+ 24	+ 21	— 2.2	— 4.3	+ 48	+ 54.9
.....	8	7	2	35	709.0	20.2	— 17	— 43	— 32	— 14	+ 20	+ 40	+ 31	+191	+131
.....	30	7	2	46	927.0	20.1	— 10	+ 3	+ 8.9	+ 21	+ 14	+ 25.3	+ 26	+131	+ 84
.....	11	5	7	60	457.7	7.6	0	+ 3	+ 25	+ 13	+ 8.3	— 5	— 5	+197	+214
.....	18	6	8	43	861.4	20.0	+ 32	+ 32	— 0.5	+ 44	+ 35	— 6.0	+ 53	+ 99	+ 29.5
.....	28	7	6	40	681.0	17.0	+ 75	+ 83	— 24.1	+135	+174	+ 16.4	+ 75	+214	+ 79.4

te constant increase in minute volume in normal infants when the mixture high in oxygen was given. Infants are listed rder of the depressive effect of the low oxygen atmosphere.

from 40 to 94 per minute in a baby who seemed perfectly comfortable and asleep.

The minute volume in high oxygen atmosphere increased in every infant compared with that in air. In the samples of gas analyzed, no reportable amount of carbon dioxide was demonstrated. The entire respiratory mechanism seemed to respond better in high oxygen atmosphere. None of the infants showed cyanosis. This is an important

reason for keeping premature or weak infants in a high oxygen atmosphere, whether they are cyanotic or not.

In all infants the minute volume in the high oxygen mixture was greater than the minute volume in air. These results indicate that the atmosphere high in oxygen as used in this experiment was always a stimulant, whereas the low oxygen mixture was often a depressant.

The rhythm in all infants changed to or remained a regular, steady, normal type 4, the high oxygen atmosphere abolishing any tendency to Cheyne-Stokes variation.

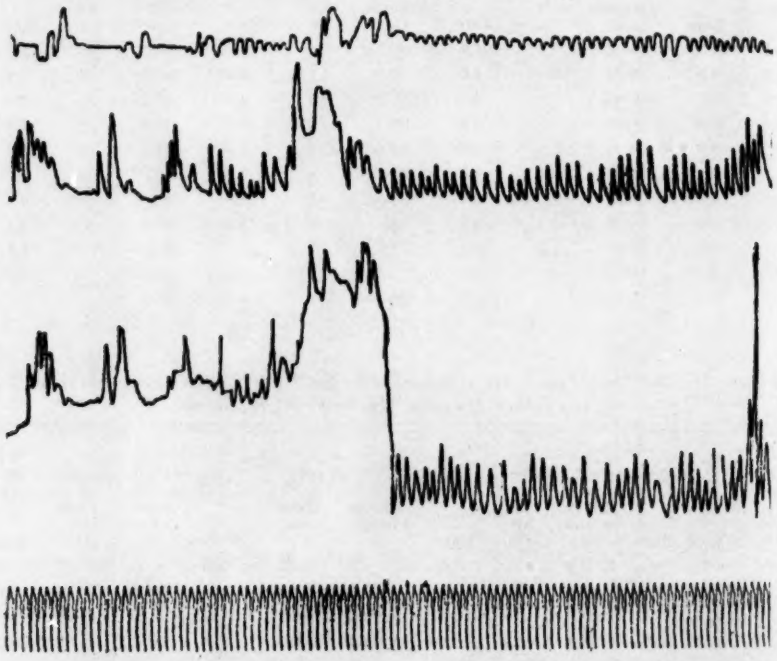

Fig. 5 (infant 9).—Breathing type 1, Cheyne-Stokes rhythm with irregularity, becoming type 4, regular, normal breathing, on administration of high oxygen concentration for forty seconds.

The chest phase in the high oxygen mixture was indeterminate, 3 showing a positive, 1 a negative and 3 an alternating phase.

OBSERVATIONS IN CARBON DIOXIDE STIMULATION

The rate or the tidal air in all 10 infants when exposed to 5 per cent carbon dioxide in 95 per cent oxygen showed a steady increase from minute to minute to the point of fussing and crying, which was reached in four to six minutes. An example of rate increase was that in infant 10 whose rates were: first minute, 54; second minute, 58; third minute, 61, and fourth minute, 72.

The minute volume under carbon dioxide stimulation was uniformly and greatly increased, the final range being 1,020 to 2,158 cc. In all instances the increase in minute volume was compared in percentage to the minute volume in air, the increase varying from 62 to 214 per cent. The figures on 3 infants are given:

Infant No.	Air		Carbon Dioxide Stimulation			
	Minute Volume, Cc.	Rate	Minute Volume, Cc.	Rate	Percentage Increase Due to Rate	Percentage Increase Due to Tidal Air
10	927	46	2,146	58	+28	72
3	413	32	1,110	32	0	100
5	628	54	1,020	42	— 9	109

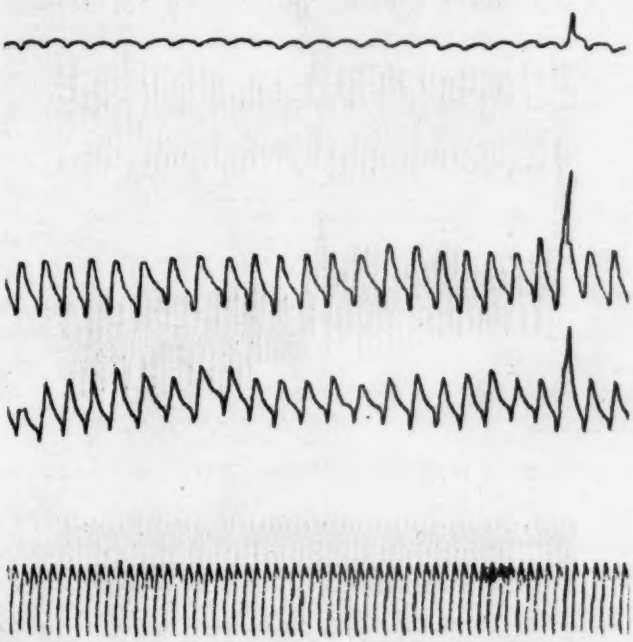

Fig. 6 (infant 3).—Breathing type 4, regular normal rhythm in high oxygen. Note tendency to cogwheel expiration.

It is evident that the increase in minute volume must be due to a combination of change in rate and change in tidal air. Three examples are given: one in which the rate per minute increased, one in which it remained constant and one in which it decreased. These are given to show the flexibility of the respiratory system even in the newborn infant.

The rhythm under carbon dioxide stimulation was steady, rapid and increasing in rate or depth, or both, until the infant awoke, constituting type 5, or extreme, supernormal breathing.

The phase of respiration was still indeterminate, not being uniform even under this extreme stimulation. The lack of uniformity is understandable, as phase depends on the strength of the ribs, cartilage and muscular action of the thorax and will remain negative part of the time until these structures are strong enough to resist the diaphragmatic pull. The infants studied had a normal, easy ingress and egress of air through the larynx.

Fig. 7 (infant 8).—Breathing type 5, stimulated rhythm. The tracing was made in the fifth minute of carbon dioxide administration. The phase is negative. Note the range of chest motion as compared with that in the other figures shown.

COMPARISON WITH THE OBSERVATIONS ON PREMATURE INFANTS

Wilson, Long and Howard [1] reported on the breathing of premature infants in air, that 25 of 33 infants showed at one time or another Cheyne-Stokes breathing. Four of these 10 newborn infants displayed this tendency, making it about half as common in full term, newborn infants as in premature infants. Wilson and his associates [1] formerly reported that 12 of 18 premature infants in a low oxygen atmosphere showed Cheyne-Stokes type of rhythm. Of the present series, 8 of 10 infants exhibited definite rhythmic breathing with periods of apnea in low oxygen atmosphere, an even more constant response than was present

in the premature infants. The former suggestion of Wilson and his co-workers was that "healthy premature infants breathed in a more normal manner in an oxygen-enriched atmosphere." Since this series of 10 infants had a higher minute volume in the atmosphere high in oxygen than in air, in every instance, it would seem evident that the regular breathing type 4 was more normal and efficient than periodic breathing.

The unexpected finding was that Cheyne-Stokes breathing in 2 instances actually gave higher minute volumes than regular normal breathing, in 1 instance an increase of 111 per cent and in the other an increase of 33 per cent. These were observed each time the infant was changed from air to the low oxygen mixture. They are instances when an immature rhythm actually performed a greater amount of work.

TABLE 5.—*Comparison of Rates and Minute Volumes*

	Rate per Minute		Minute Volume, Cc.		Minute Volume, Cc./Lb.		Tidal Air, Cc.	
	Average	Range	Average	Range	Average	Range	Average	Range
Murphy and Thorpe [3]	43.1	24 to 116	721	433 to 1,413	.....	.....	16.7	10 to 27
Shaw and Hopkins [6]	49	58 to 67	600	696 to 795	193.1	121 to 323	12.3	4.5 to 17.2
Deming and Washburn [2]	41	24 to 76	1,078	354 to 2,007	131.0	59 to 230	27.0	9.7 to 53.1
Deming and Hanner [7]	44	16 to 93	851	225 to 1,835	127.0	38 to 248	19.8	9.7 to 30.5
Howard and Bauer	48	32 to 67	731	413 to 1,127	113.5	80.5 to 167.1	16.5	6.9 to 26.8

COMPARISON WITH RESULTS IN THE LITERATURE

The articles dealing with rate and rhythm of respiration were thoroughly summarized by Smith.[5] The reports of volume of air breathed per minute are pertinent to this study, actually forming the basis for it. Murphy and Thorp [3] used the body plethysmograph in measuring tidal air and minute volumes of newborn, full term babies. Shaw and Hopkins,[6] working at the same time as Murphy and Thorpe, studied premature infants by this method, the two articles having been published the same month. Deming and Washburn [2] and Deming and Hanner [7] used an apparatus so accurate that ours was copied from it with only minor variations. The average results from the studies and a comparison with our figures are shown in tabular form.

6. Shaw, L. A., and Hopkins, F. R.: The Respiration of Premature Infants, Am. J. Dis. Child. **42**:335 (Aug.) 1931.

7. Deming, J., and Hanner, J. P.: Respiration in Infancy: II. A Study of the Rate, Volume and Character of Respiration in Healthy Infants During the Neonatal Period, Am. J. Dis. Child. **51**:823 (April) 1936.

Our results actually were nearer to those of Murphy and Thorpe [3] than to any other reported measurements, and we noted that our spirometer, as we had it set up showed the same type of difference in calibration which they recorded, that is, with faster rates the same pointer excursion indicated less actual air exchange, the pointer moving slightly farther when traveling rapidly.

A study of rhythm and rate was done by Wilson, Long and Howard [1] on premature infants, with special reference to the the effect of low and high oxygen atmospheres and also to that of increased carbon dioxide content. The present study is an extension of that work. This study is more complete than former studies, as we obtained quantitative measurements of the tidal air and minute volume and the rate on newborn infants breathing air, low oxygen and high oxygen mixtures and carbon dioxide and oxygen. At the same time, we were able to get partially quantitative measurements of the chest and abdominal movements. The production of Cheyne-Stokes breathing with a low oxygen atmosphere and its abolishment with an atmosphere high in oxygen were sufficiently striking to consider this as confirming the findings of Wilson, Long and Howard.[1] The remarkable stimulation obtained with carbon dioxide adds confirmation of a quantitative nature to that which has so often been observed clinically. The point to be added is that these responses are not limited to premature infants but are just as striking in full term infants.

Bauer [4] wrote concerning the variation of chest and abdominal movement in respiration, and our results are a corroboration of and further contribution to his work.

COMMENT

The infants were normal and healthy as far as could be judged from physical examination and were not disturbed by any of the determinations of rate and minute volume, as the records were taken only during sleep. Our records in air agree well with those previously made and we demonstrated the irregularities which have been described earlier. Six infants showed regular type 4 breathing in air, and 4 infants displayed Cheyne-Stokes rhythm, type 2. When placed in a low oxygen atmosphere, all infants changed to a more immature rhythm or remained the same. If an infant revealed any rhythmic tendency in air, this was exaggerated in the low oxygen mixture. The production of rhythmic Cheyne-Stokes breathing probably depends on the blood hydrogen ion concentration, which, if ineffective in stimulating the medullary centers, allows the low oxygen mixture to stimulate the carotid sinus, a secondary or emergency mechanism which operates to produce the rhythm. Other factors which operate are a persistence of fetal type hemoglobin, which has a greater affinity for oxygen than adult hemoglobin, a change in the permeability of the red cell membrane,

with similar effect, and a deficiency in carbonic anhydrase as slowing the chemical reaction of carbonic acid to carbon dioxide and water. The reasons for the occurrence of Cheyne-Stokes breathing in premature infants, and its easy production in full term infants was explained by Wilson, Long and Howard [1] on this basis:

> . . . The stimulus of such an atmosphere produces an intermittent respiration because the supply of the arterial oxygen is quickly depleted or replenished by small variations in respiration.

They added a note of caution: "We do not believe that the significance of such periodic breathing can always be clearly established."

The shallow breathing of alkalosis, with periods of apnea, such as occurs in pyloric stenosis, is not unlike the type 1 Cheyne-Stokes breathing. The medullary centers themselves may be disturbed by the low supply of oxygen so that their threshold of stimulation is increased. We question whether one is justified in terming Cheyne-Stokes a "less efficient" form of breathing than normal. Both rhythms were measured as to minute volume in each of 4 infants. Rhythmic breathing produced a lower minute volume in 2 and a higher minute volume in 2 infants. Cheyne-Stokes rhythm has been accepted almost by common consent as a "less efficient" type of respiration, but twice it has been shown to be more efficient than normal regular breathing. Nevertheless, it is less dependable and a sign of impending trouble, which was quickly abolished in all cases by giving the high oxygen mixture. The administration of this mixture caused a distinctly more effective respiration, as evidenced by the uniform increase in minute volume in all subjects of this study. It can be presumed that the oxygen saturation of the infants was raised, by the change from air to the high oxygen atmosphere, though none showed any cyanosis or distress, unless type 2 breathing may be taken for a "distress" sign. This seems to indicate that a high oxygen mixture should be administered in the newborn period for very minor disturbances of the respiration or breathing rhythm.

The administration of 5 per cent carbon dioxide in 95 per cent oxygen was observed to cause a definite increase in regularity, tidal air and minute volume. Whether the rate increased depended on the tidal air, the two factors being somewhat reciprocal. The increases in minute volume were from 62 to 214 per cent over the same value in air. This stimulant was used only two to six minutes because it produced fussing and crying, during which no record could be made. In 6 infants the increase in minute volume was 100 per cent or more, showing carbon dioxide to be a violent stimulant. The Kussmaul type of breathing which occurs in clinical acidosis is not unlike that which we obtained by giving carbon dioxide and oxygen. It is possible that both

gases are so extremely important individually to the normal functions of the body that the irregularities observed are the natural attempt to quantitate the exchange of one gas with reference to the other so as to satisfy the body needs for either respectively. With this in mind, we are planning a future research in which we shall employ the oximeter, estimations of blood hydrogen ion concentration, administration of 5 per cent carbon dioxide in air and any other measures, so far as they may be practical in this type of work. It is evident that the concentration of oxygen and of carbon dioxide are both important to the baby's economy and probably cannot be so completely divorced as has been the tendency recently in explanations of the irregularities of breathing in infants.

Regardless of the cause or physiologic significance of Cheyne-Stokes breathing or of the fact that it is often present in premature and full term, normal infants, two outstanding facts remain: It is seen in connection with serious conditions, and the administration of a high oxygen mixture seems to relieve the condition causing it to the point of abolishment. This, in particular, gives us reason to reiterate and reemphasize the contention made by one of us [8] seventeen years ago: Oxygen is the most valuable single therapeutic agent available for a premature or full term, newborn infant who is showing any evidence of respiratory difficulty, and it should be used early and generously. We feel that our observations amply support this view.

SUMMARY

1. The rate of respiration, the irregularities of rhythm, the minute volume and the tidal air volume were studied in 10 normal, newborn infants in air, 12 per cent oxygen, 70 per cent oxygen and 5 per cent carbon dioxide in oxygen.

2. The average rates were 46.5 per minute in air, 44.5 per minute in the low oxygen atmosphere, 53 per minute in the high oxygen atmosphere and 51.3 per minute in the mixture of carbon dioxide in oxygen.

3. The rhythm of breathing was irregular and was classified from the most immature type to a supernormal type: type 1, Cheyne-Stokes with irregularity; type 2, Cheyne-Stokes with apnea; type 3, rhythmic breathing but without apnea; type 4, regular normal; type 5, supernormal, stimulated.

4. The average minute volumes were 731.3 cc. in air; 792.3 cc. in the low oxygen mixture; 993.9 cc. in the high oxygen mixture and 1,660.0 cc. in the mixture of carbon dioxide and oxygen.

8. Bauer, A. R.: A Combination Resuscitator and Incubator for Newborn Infants, J. A. M. A. **108**:1874 (May 29) 1937.

5. The average tidal air volume was 16.5 cc. in air; 18.7 cc. in an atmosphere low in oxygen; 20.7 cc. in an atmosphere high in oxygen, and 33 cc. in an atmosphere of carbon dioxide and oxygen.

6. Immature type 2 breathing occurred in 4 newborn babies in air, making it one-half as common as in premature infants. Immature type 1 or type 2 breathing occurred in 8 of 10 babies in the low oxygen atmosphere, making this at least as common as in premature infants.

7. The infants breathed an average of 113.5 cc. per pound per minute when breathing air, 124.5 cc. per pound in the mixture low in oxygen, 153.2 cc. per pound in the mixture high in oxygen and 259.7 cc. in the mixture of carbon dioxide and oxygen.

8. Irregular breathing in early infancy should be treated with a mixture high in oxygen even more than at present, as such an atmosphere regularly increases breathing volume and has a steadying effect on the rhythm of respiration.

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STANDARD, UNIPOLAR LIMB AND PRECORDIAL LEADS IN CHILDREN AND ADOLESCENTS WITH INACTIVE RHEUMATIC FEVER

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IN CHILDREN the electrocardiogram has proved of value in establishing diagnoses of active carditis and congenital cardiac disease. In the quiescent stage of rheumatic heart disease, however, standard leads often yield normal tracings in children with enlarged hearts and obvious myocardial involvement.

In adults, precordial, as well as standard, leads have given valuable information in regard to hypertrophy of individual chambers of the heart.[1] It was thought possible, therefore, that this technic might also be useful in studying rheumatic children and adolescents.

MATERIAL

One hundred and fifty-six rheumatic subjects, 98 boys and 58 girls, were studied. Of these, 144 were children ranging in age from 6 to 15 years, who were observed in a convalescent home for periods of four months to four years, and 12 were adolescents followed in the outpatient department. All the patients gave histories of one or more attacks of rheumatic fever and, with one exception, were in the quiescent stage of the disease. Of the 156, 44 had definite and 25 suspected organic heart disease, while the condition of 87 was classified as potential and possible rheumatic heart disease, according to the criteria of the New York Heart Association.[2]

From Irvington House.

This study was aided by funds raised through the cooperation of Mr. Ralph B. Rogers.

1. (*a*) Gubner, R., and Ungerleider, H. E.: Electrocardiographic Criteria of Left Ventricular Hypertrophy: Factors Determining Evolution of Electrocardiographic Patterns in Hypertrophy and Bundle Branch Block, Arch. Int. Med. **72**:196 (Aug.) 1943. (*b*) Wilson, F. N.; Johnson, F. D.; Rosenbaum, F. F.; Erlanger, H.; Kossmann, C. E.; Hecht, H.; Cotrim, N.; DeOlivereira, R. M.; Scarsi, R., and Barker, P. S.: The Precordial Electrocardiogram, Am. Heart J. **27**:1, 1944. (*c*) Goldberger, E.: Unipolar Lead Electrocardiography, Philadelphia, Lea & Febiger, 1947. (*d*) Myers, G. B.; Klein, H. A., and Stofer, B. E.: The Electrocardiographic Diagnosis of Right Ventricular Hypertrophy, Am. Heart J. **35**:1, 1948.

2. Nomenclature and Criteria for Diagnosis of Diseases of the Heart, ed. 4, New York, New York Heart Association, 1939.

METHODS

In addition to standard leads, the chest leads, V_1, V_2, V_3, V_4, V_5 and V_6 were taken from the six points recommended by the American Heart Association.[3] In some instances V_7, V_8 and V_{8R} were also taken. All the tracings were made in the reclining position. In taking the precordial leads, each site was rubbed individually with electrode jelly immediately before the tracing was recorded, to reduce conduction over the surface of the thorax as much as possible.[4] Augmented unipolar limb leads (aV_R, right arm; aV_L, left arm and aV_F, left leg) were also taken, according to Goldberger's modification of Wilson's technic.[5] In most instances two or more tracings were recorded for each patient.

CRITERIA

Electrical Position of the Heart.—As suggested by Goldberger, the electrical positions were classified as vertical, horizontal and intermediate by means of the augmented unipolar limb leads. Vertical hearts show small q and large R waves (qR) in tracings of the unipolar limb lead from the left leg, while horizontal hearts show a qR pattern in the unipolar limb lead from the left arm (aV_L) and intermediate hearts, qR complexes in both aV_F and aV_L. The q wave is often minute, and some tracings are difficult to interpret. In most instances, however, the three electrical positions of the heart can be differentiated.

Left Ventricular Hypertrophy.—In the precordial leads, left ventricular hypertrophy is associated with small R and deep S waves in leads facing the epicardium of the right ventricle. The R waves become taller and are often accompanied with deep Q waves in leads facing the epicardium of the left ventricle. The peak of R occurs late in the QRS interval. The tracings were also examined for widened QRS intervals (0.10 second or more), depressed S-T segments and inverted T waves in leads from the left side of the precordium. In patients with vertical hearts, the occurrence of high voltage in leads II and III (the sum of the R waves in leads II and III equaling 40 mm. or more and the R wave of aV_F measuring one half of this amount) was noted. In children with horizontal hearts, high voltage was considered present when the sum of the R waves in lead I and the S waves in lead III was greater than 25 mm. and the R wave of aV_L was 13 mm. or more.[1a,c]

Right Ventricular Hypertrophy.—Precordial leads are essential to establish the electrocardiographic diagnosis of right ventricular hyper-

3. The Standardization of Precordial Leads: Supplementary Report, Am. Heart J. **15**:235, 1938.

4. Ziegler, R. F.: A Note on the Importance of Proper Technique in the Recording of the Precordial Electrocardiogram, Am. Heart J. **35**:769, 1948.

5. Goldberger, E.: A Simple, Indifferent, Electrocardiographic Electrode of Zero Potential and a Technique of Obtaining Augmented, Unipolar, Extremity Leads, Am. Heart J. **23**:483, 1942.

trophy. The observations of a qR pattern or tall R wave at V_1 and V_2, accompanied with inverted T waves, and R waves tall in relation to the S waves were considered characteristic. The R waves tend to become smaller in leads from the left side of the precordium. In some instances when the QRS complexes at V_1 and V_2 were not typical and the QRS pattern at V_5 and V_6 suggested right ventricular hypertrophy, lead V_{3R} (taken to the right of the sternum at a site comparable to V_2 on the left) usually showed a qR pattern indicative of right ventricular hypertrophy. The interval from the Q wave to the peak of the R wave (intrinsicoid deflection) was prolonged (0.03 to 0.04 second) at V_1 and was decreased at V_6.

Auricular Hypertrophy.—Auricular hypertrophy was considered present when the duration of the P wave was 0.10 second or more, irrespective of whether notching or high voltage was also observed.[6]

P-R Interval.—In patients with organic rheumatic heart disease, permanently prolonged P-R intervals in most instances are probably due to structural damage of the conduction system. P-R intervals of 0.18 second or more in apparently normal children and of 0.20 second or more in healthy young adults have been reported and in the opinion of some authors are due to increased vagal tone rather than to injury of the conduction fibers.[7] In children with equivocal rheumatic histories or in rheumatic children with normal cardiac findings, a prolongation of the P-R interval in itself was not considered definite evidence of organic heart disease.

RESULTS

Electrical Position of the Heart.—Since the electrical position of the heart influences the standard and the precordial leads, augmented unipolar limb leads were taken on every subject. As shown in table 1, the variations in the electrical position of the heart in patients with definite or suspected organic heart disease did not differ significantly from the position in those without cardiac involvement.

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6. Ashman, R.: Electrocardiography in Children, Mod. Conc. Cardiovasc. Dis., 1938, vol. 7, no 1.

7. Ferguson, D. O., and O'Connell, J. T.: Cardiovascular Observations, Including a Series of Electrocardiograms of 1812 Men Without Heart Symptoms, U. S. Nav. M. Bull. **24**:860, 1936. Seham, M.: The Electrocardiogram in Normal Children, Am. J. Dis. Child. **21**:247 (March) 1921. Burnett, C. T., and Taylor, E. L.: Electrocardiograms on One Hundred and Sixty-Seven Average Healthy Infants and Children, Am. Heart J. **11**:185, 1936. Lincoln, E. M., and Nicolson, G. H. B.: Hearts of Normal Children: Electrocardiographic Records, Am. J. Dis. Child. **35**:1001 (June) 1928. Reyersbach, G., and Kuttner, A. G.: Studies on Auriculoventricular Conduction Time of Normal Children and of Rheumatic Children Without Signs of Rheumatic Activity, Am. Heart J. **20**:53, 1940.

Deviation of the Electrical Axis.—Deviation of the electrical axis is relatively uncommon in children and, therefore, is often considered indicative of cardiac enlargement. Of the 87 children with normal cardiac findings (with potential and possible rheumatic heart disease), 13 had slight deviation of the electrical axis in the standard leads; 11 showed left and 2 right axis deviation.

TABLE 1.—*Electrical Position of the Heart*

Number of Patients	Cardiac Status	Roentgenographic Enlargement	Position of Heart		
			Vertical	Horizontal	Intermediate
87	Potential and possible heart disease	..	50	26	11
25	Organic heart disease?.....	+?	13	7	5
7	Organic heart disease.....	..	3	4	0
37	Organic heart disease.....	+	23	9	5
156			89	46	21

TABLE 2.—*Relation of Axis Deviation to the Electrical Position of the Heart in Persons with Potential and Possible Rheumatic Heart Disease*

Case Number	Age, Yr.	Sex	Roentgenographic Enlargement	Electrical Position	Axis Deviation	Comment
1.....	12	M	None	Horizontal	Left *	T_3 varied
2.....	7	M	None	Horizontal	Left	T_3 diphasic
3.....	12	M	None	Horizontal	Left	T_3 inverted
4.....	7	M	None	Horizontal	Left *	T_3 varied
5.....	13	M	None	Horizontal	Left	T_3 inverted
6.....	10	M	None	Horizontal	Left	T_3 diphasic
7.....	11	M	None	Horizontal	Left	
8.....	12	M	None	Horizontal	Left	
9.....	10	M	None	Horizontal	Left †	
10.....	11	F	None	Intermediate	Left †	T_3 inverted
11.....	13	F	None	Intermediate	Left	
12.....	13	M	None	Vertical	Right	
13.....	11	M	None	Vertical	Right	

* Degree of deviation varied with respiration.
† Axis deviation disappeared with the growth of the child.

Left Axis Deviation: The electrical position of the heart in 9 of these 11 children was horizontal and in 2 intermediate. In most instances, the degree of axis deviation and of inversion of the T waves in lead III varied with respiration and from day to day. In 2 obese girls, who grew taller and lost weight during the period of observation, the tendency to left axis deviation disappeared. In the remainder, it persisted to the same degree in every tracing. In all these children, deviation of the axis to the left was correlated with the electrical position of the heart, which in the majority was horizontal. Unipolar limb and

precordial leads showed normal tracings, and there was no clinical or roentgenologic evidence of enlargement.

Nine other children with definite or suspected organic heart disease and with little, if any, enlargement of the left ventricle were found to have left axis deviation. In 6 the heart was horizontal and in 3 intermediate. In these children the tendency to left axis deviation also appeared to be correlated with the electrical position of the heart.

Four children with severe rheumatic heart disease and cardiac enlargement showed slight or definite left axis deviation. In 3 this

TABLE 3.—*Left Axis Deviation in Persons with Definite and Suspected Organic Heart Disease*

Case No.	Age, Yr.	Sex	Diagnosis	Roentgenographic Enlargement	Electrical Position	Left Axis Deviation	Comment
1	12	M	Mitral insufficiency Mitral stenosis Aortic involvement	Left ventricle	Horizontal	++	R aV_L 14
2	12	M	Aortic involvement	Negative	Horizontal	±	
3	9	M	Aortic involvement	Negative	Horizontal	+	
4	11	M	Mitral insufficiency Mitral stenosis Aortic involvement	Moderate	Horizontal	±	T_3 varied
5	14	F	Mitral insufficiency ? Mitral stenosis	?	Horizontal	+	T_3 inverted
6	12	M	Mitral insufficiency Mitral stenosis	Marked	Intermediate	±	
7	13	F	Mitral insufficiency Mitral stenosis	Marked	Intermediate	±	
8	18	F	Mitral insufficiency *	? Left ventricle	Horizontal	++	T_3 diphasic
9	17	M	Mitral insufficiency *	? Left ventricle	Horizontal	++	T_3 inverted
10	20	F	Mitral insufficiency *	? Left ventricle	Horizontal	+	
11	10	M	Mitral insufficiency *	? Left ventricle	Intermediate	+	T_3 diphasic
12	9	M	Mitral insufficiency *	? Left ventricle	Intermediate	±	T_3 inverted
13	13	M	Mitral insufficiency *	? Left ventricle	Intermediate	±	T_3 inverted

* The diagnosis of mitral insufficiency in these patients was based on the intensity of the apical systolic murmur in the absence of definite cardiac enlargement (Kuttner, A. G., and Markowitz, M.: Am. Heart J. 35 : 718, 1948).

observation was transitory. In the fourth child, coincident with the development of an aortic diastolic murmur, left axis deviation persisted and became more pronounced. The standard, unipolar and precordial leads of this patient showed high voltage.

Right Axis Deviation: Of the 87 children with potential and possible rheumatic heart disease, 2 showed right axis deviation (cases 12 and 13 in table 2). Both these children had hearts of the vertical type with definite clockwise rotation. Unipolar limb and precordial leads did not show right ventricular hypertrophy. There was no clinical evidence of congenital or rheumatic heart disease in either of these 2 patients, and roentgenologic examination of the heart failed to reveal any abnormality of size or contour. The right axis deviation in both

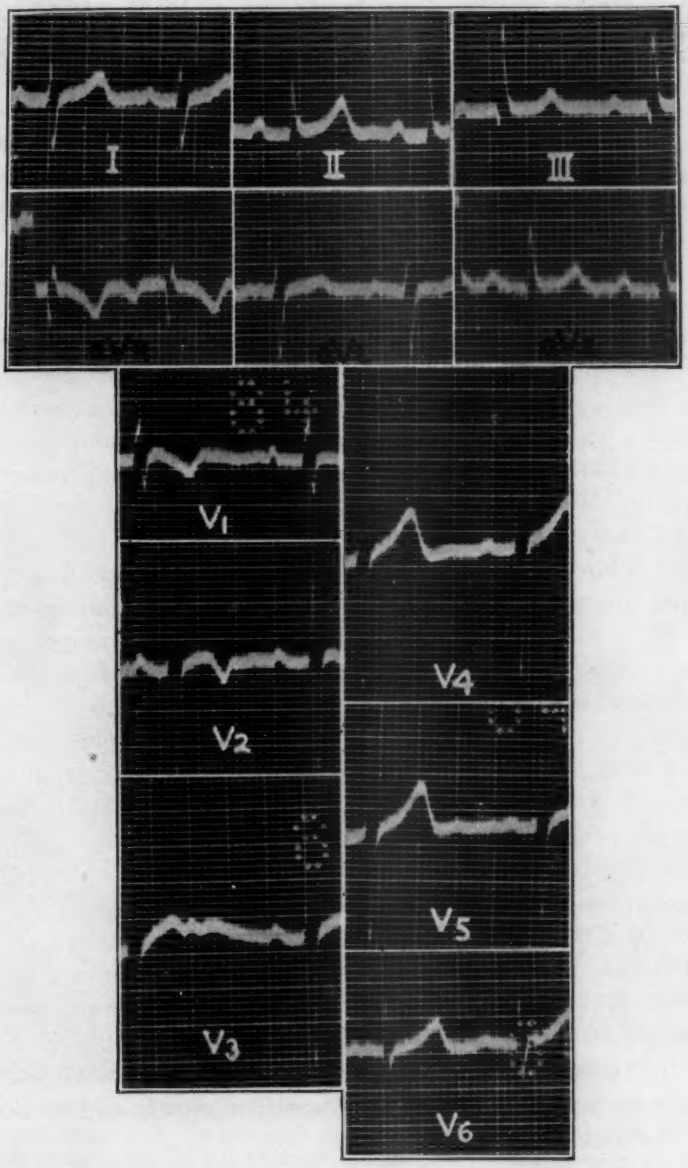

Fig. 1.—Electrocardiographic studies on a boy, 11 years of age, who had two attacks of rheumatic polyarthritis. The cardiac signs are normal, with right axis deviation. The heart was vertical with decided clockwise rotation. Precordial leads are not indicative of right ventricular hypertrophy.

these children, therefore, was considered to be a normal variant, related to the electrical position of the heart.

Left Auricular Hypertrophy.—In children, in contrast to adults, the significance of apical diastolic murmurs is often difficult to interpret. Although it is generally agreed that loud, rumbling, crescendo diastolic murmurs may be taken as definite evidence of a stenotic deformity of the mitral valve, in children the diagnosis of mitral stenosis is frequently based on a low-pitched murmur or rumble heard in mid or late diastole, Bland, Jones and White pointed out that the latter type of murmur may disappear and is probably due to temporary cardiac dilatation associated with activity of the rheumatic infection.[9]

From the prognostic point of view, it is often more important to determine the extent of myocardial involvement than the degree of valvular deformity. Left auricular enlargement, as indicated by the esophagram, is primarily due to dilatation, which may or may not be accompanied with hypertrophy. The presence of an inflammatory reaction or an actual increase in the muscle mass would be reflected more accurately by interference with conduction, as indicated by the increased duration of the P wave, than by the esophagram.

In 20 children, who had P waves of 0.10 to 0.14 second, with one exception, enlargement of the left auricle was demonstrable by esophagram. The duration of the disease in these 20 subjects ranged from a minimum of two to a maximum of eleven years. In 9 of these 20 children, in whom the width of the P wave was 0.12 second or more, enlargement of the left auricle varied from 1 plus to 3 plus, indicating that there was no direct correlation between the degree of dilatation and the impairment of conduction. Auricular hypertrophy in these 20 patients was probably not associated with right ventricular enlargement, since the unipolar precordial leads in each of them was normal.

In 4 children who were considered to have apical diastolic murmurs the duration of the P wave was less than 0.10 second and the esophagram showed nothing abnormal. The presence of diastolic murmurs in these 4 patients was confirmed by stethographic tracings of the heart sounds.[10] In these 4 patients, in whom the duration of the disease varied from two to nine years, it seems possible that the lesions were chiefly valvular, with little or no involvement of the auricular muscle and no demonstrable dilatation of the left auricle.

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8. Footnote deleted.

9. Bland, E. F.; Jones, T. D., and White, P. D.: Disappearance of Physical Signs of Rheumatic Heart Disease, J. A. M. A. **107**:569 (Aug. 22) 1936.

10. The stethographic tracings were taken through the courtesy of the Cambridge Instrument Company, Inc., New York on a simpli-trol® portable electrocardiograph-stethograph.

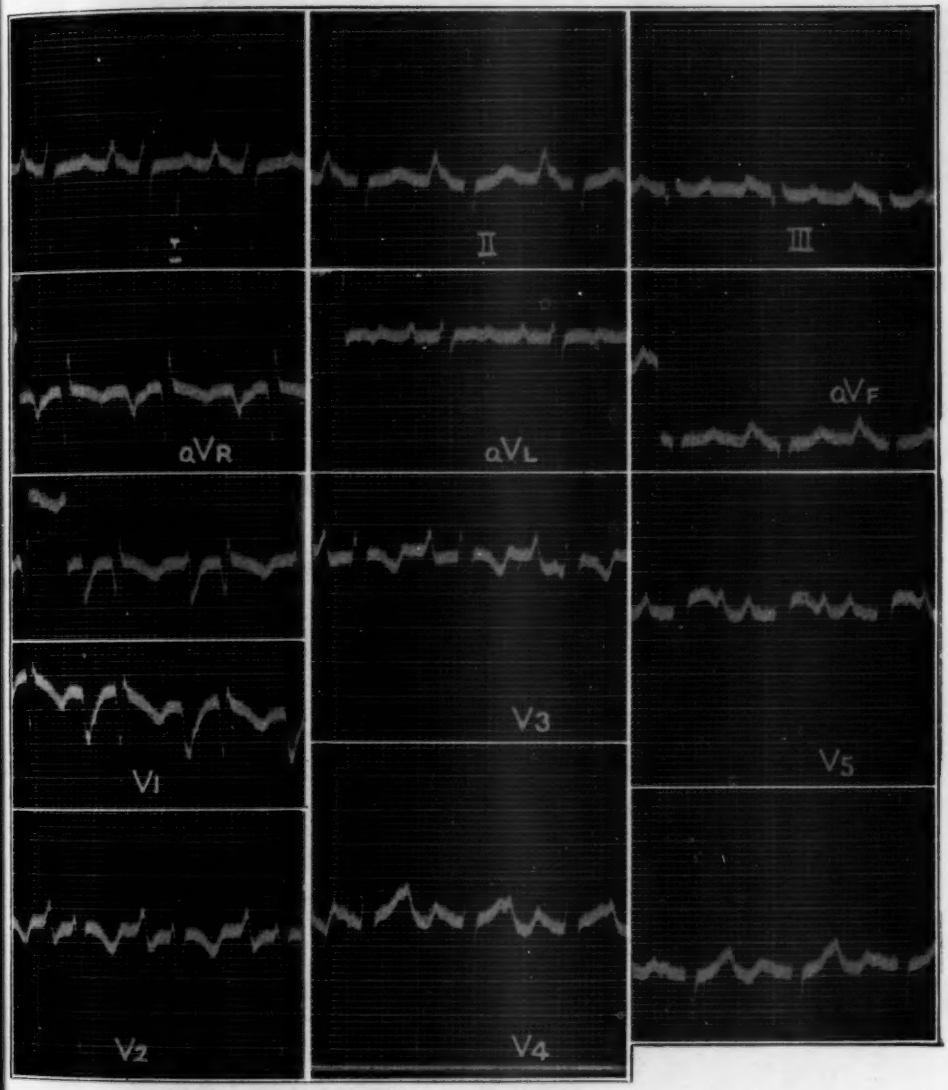

Fig. 2.—Electrocardiographic studies on a boy, 13 years of age, who had mitral insufficiency and stenosis with pronounced cardiac enlargement. Chronic congestive failure and enlargement of the liver were also present, with right axis deviation. The heart was in vertical position with decided clockwise rotation (deep S wave at V_6). The precordial leads, including V_{2R}, are not indicative of right ventricular hypertrophy. The R wave of a V_F measures 23 mm. T waves at V_1, V_2, V_3 and V_4 are inverted. The Q wave is absent at V_4, probably because the electrode was not over the left ventricle.

In 2 children, in whom the apical diastolic murmurs were inconstant, stethographic tracings of the heart sounds showed no abnormal deflections during diastole. Yet in 1 of these patients the duration of the P wave was 0.10 second and the esophagram showed abnormality, and in the other child the P wave was 0.11 second and the esophagram normal, suggesting that in these 2 children there may have been some impairment of auricular conduction without significant valvular deformity.

Ventricular Hypertrophy.—Gubner and Ungerleider studied adults with left axis deviation and long-standing hypertensive heart disease in whom the presence of left ventricular hypertrophy could be assumed. They reported that in such persons the sum of the R waves in lead I and the S waves in lead III equaled or exceeded 25 mm. These authors concluded that this electrocardiographic sign alone, without other changes, was the earliest indication of left ventricular hypertrophy and that the electrocardiogram in this respect is slightly more sensitive than the teleroentgenogram.[1a]

Goldberger, using the criterion suggested by Gubner and Ungerleider, stated that in patients with horizontal hearts a similar deduction can be made from the augmented unipolar limb leads; thus, since aV_L equals $\frac{\text{lead I} + \text{lead III}}{2}$, an R wave of 13 mm. or more in this lead is an indication of left ventricular hypertrophy.[1c] Similarly, in patients with vertical hearts, high voltage (the R wave equaling 20 mm. or more as defined by the New York Heart Association) in leads II and III has the same significance.[2] According to Goldberger, in this type of heart left ventricular hypertrophy is present when the sum of R waves in leads II and III is 40 mm. or more, and the height of R waves at aV_F would, therefore, be half of this amount.

At present, the criteria for the diagnosis of left ventricular hypertrophy on the basis of high voltage in hearts of the intermediate type have not been defined.

Augmented unipolar limb leads and precordial leads were studied as a means of determining ventricular hypertrophy.

High Voltage in Children with Electrically Vertical Hearts: In 21 children with organic heart disease and cardiac enlargement as shown by teleroentgenogram, the electrical position of the heart was vertical. The tracings of 11 of these 21 showed an R wave of 20 mm. or more in aV_F, in one instance accompanied with right axis deviation.

Eighteen children and adolescents, with definite or suspected organic heart disease and little, if any, cardiac enlargement on roentgenologic examination, had electrically vertical hearts. Five of the 18 showed high voltage in aV_F.

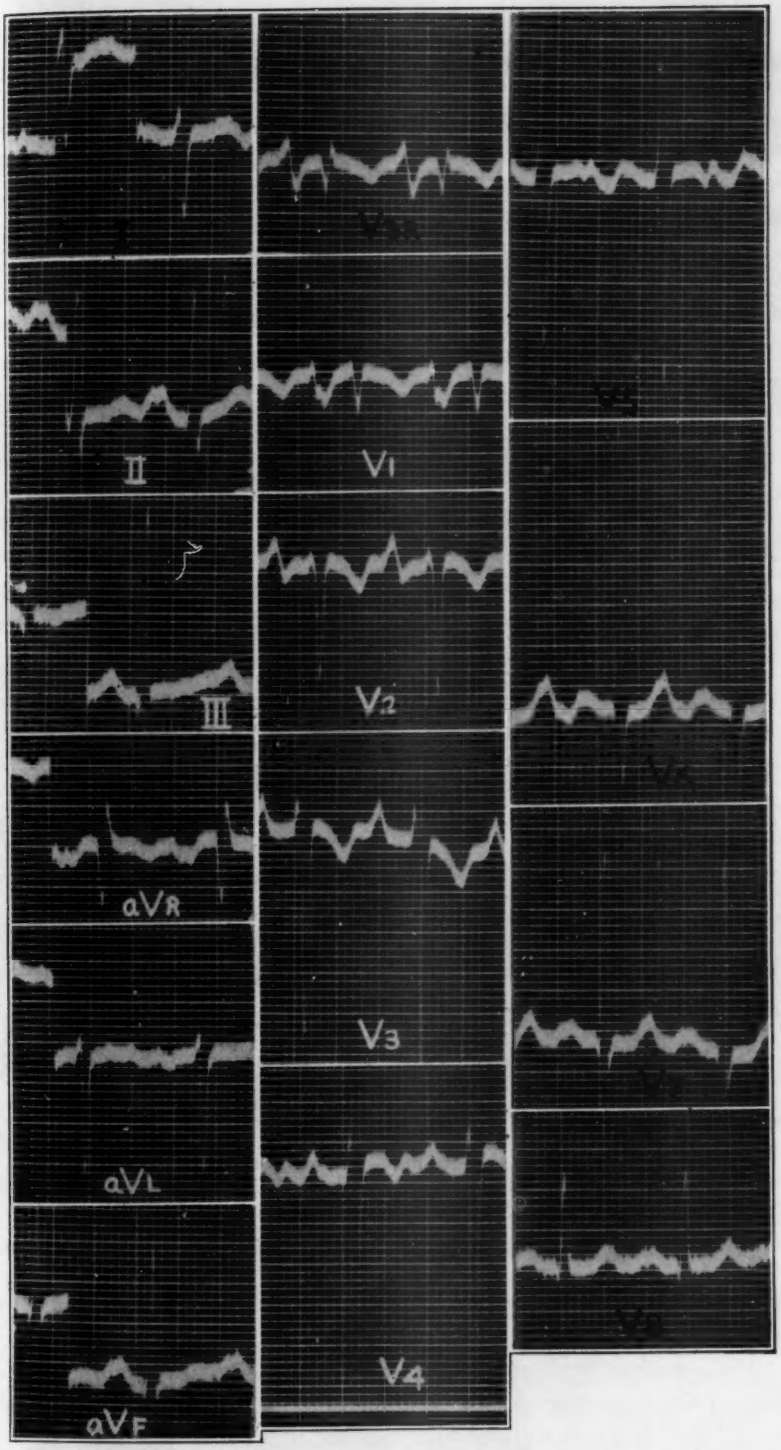

Fig. 3.—Another tracing made on the same patient. Inverted T waves are present in this patient at V_1 through V_3. There is inversion at V_4 or V_5 which was variable, depending on the rotation of the heart and the position of enlarged liver rather than on rheumatic activity. At V_6, V_7 and V_8, q waves are present, with tall R and upright T waves.

In 50 children with normal cardiac findings, whose condition was classified as potential and possible rheumatic heart disease, the electrical position of the heart was vertical. High voltage was not observed in the tracings of any of these children.

High Voltage in Patients with Electrically Horizontal Hearts: Nine children with organic heart disease and cardiac enlargement by teleroentgenogram had horizontal hearts. In only 1 of these was high voltage present at aV_L. On the other hand, the precordial leads of

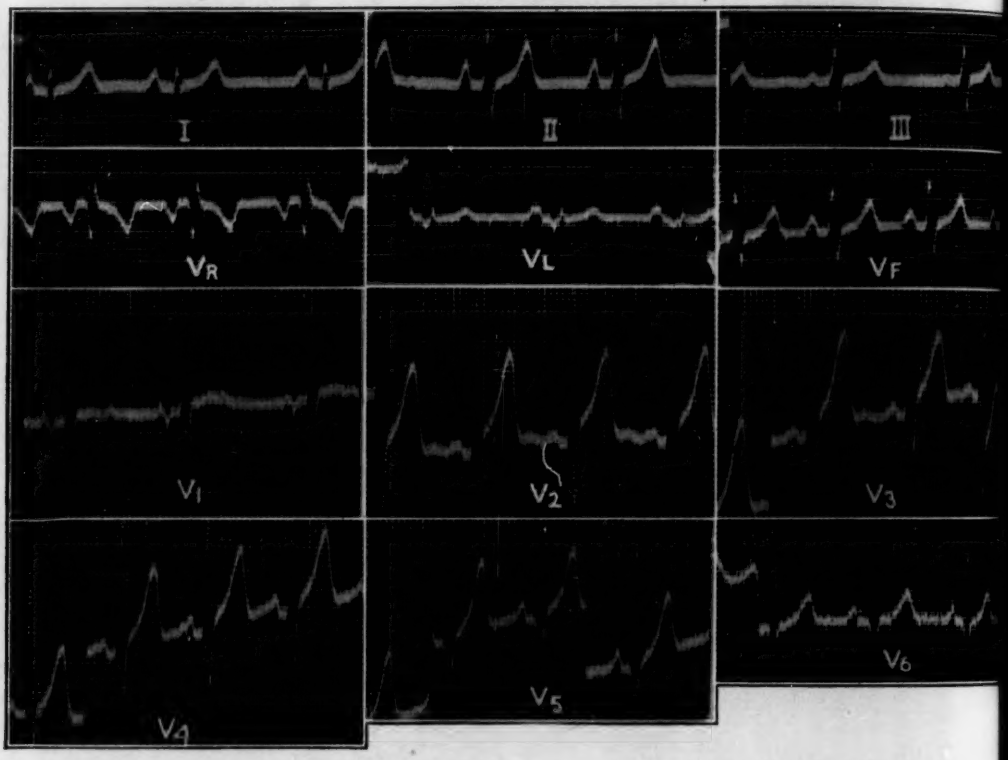

Fig. 4.—Electrocardiographic studies on a boy 14 years of age. He had an eleven year history of rheumatic fever. Mitral insufficiency and stenosis were present with slight cardiac enlargement. The S waves in leads II and III are evident. The heart was horizontal. High voltage activity in the R waves at V_1 and V_2 indicate right ventricular hypertrophy.

another child in this group showed evidence of right ventricular hypertrophy.

Five children with mitral or aortic lesions, but no definite cardiac enlargement by roentgenologic examination, had hearts of the horizontal type. None of these showed high voltage in aV_F.

Twenty-six children, whose conditions were classified as potential and possible rheumatic heart disease, had horizontal hearts. High voltage in aV_F was not observed in the tracings of any of these subjects.

In none of the 17 children with high voltage in aV_F or in aV_L were widening of QRS intervals or depressed S-T segments, accompanied with inverted T waves, observed in the leads facing the left ventricle. Although these generally accepted criteria of left ventricular hypertrophy were lacking, the pattern of the precordial leads of these children was consistent with that observed in proved cases of left ventricular hypertrophy. It is of interest, furthermore, that in the majority of children with organic heart disease, irrespective of whether high voltage was present at aV_F or aV_L, deeper S waves were observed in leads from the right side of the precordium and taller R waves from leads facing the left ventricle than in tracings of children with no evidence of cardiac involvement.

Scarring of the Conduction System: Permanently prolonged P-R intervals (0.23 to 0.26 second) were observed in only 2 of the 44 children with organic heart disease.

COMMENT

An attempt has been made to evaluate the electrocardiogram as an aid in the diagnosis of organic heart disease in rheumatic children and adolescents in the quiescent stage of the disease. Standard, augmented unipolar limb and precordial leads were taken. In addition to changes in QRS intervals, S-T segments and T waves, the tracings were examined for the presence of high voltage in the augmented unipolar limb leads and for patterns indicative of left or right ventricular hypertrophy in the precordial leads. Prolongation of the P-R interval and widening of the P wave were also noted.

In children the significance of apical diastolic murmurs is often difficult to evaluate. The presence of left auricular hypertrophy, therefore, may be of aid in establishing a diagnosis of mitral stenosis. Enlargement of the left auricle as determined by the esophagram is frequently equivocal and observers vary in their interpretation. The prolongation of the P wave to 0.10 second or longer is a more objective means of determining auricular hypertrophy. Notching, without widening of the P wave, varied greatly in tracings taken on the same patient at different times and, therefore, was not considered a reliable indication of auricular hypertrophy. Peaking of the P wave, according to Myers and his co-workers, varies with the position of the diaphragm and by itself does not indicate hypertrophy.[14]

Because the standard leads are often normal, even in children with greatly enlarged hearts and obvious myocardial involvement, there has been a tendency to exaggerate the importance of minor electrocardiographic changes. Since axis deviation in children is relatively uncommon, it is sometimes interpreted as evidence of cardiac enlargement. It

was not until the studies of Master,[11] Wilson [1b] and Goldberger [1c] pointed out the importance of the electrical position of the heart on axis deviation that its significance was properly evaluated.

The determination of the electrical position of the heart by means of the augmented limb leads of Goldberger is of aid both in right and in left axis deviation. It varies independently of body build and of the cardiac silhouette: For example, the electrical position of the heart of an asthenic person may be horizontal and that of a heart typically transverse on teleroentgenogram, vertical. Left axis deviation of varying degrees occurs as a normal variant in persons in whom the electrical position of the heart is horizontal, often accompanied with transitory inversion of the T wave in lead III. Pronounced right axis deviation may occur in children with normal cardiac findings if the heart is vertical and rotated decidedly in a clockwise direction. In such persons unipolar precordial leads should be taken to exclude the possibility of right or left ventricular hypertrophy.

In contrast to adults, inversion of the T waves at V_1, V_2 and V_3 is not unusual in unipolar precordial leads and is especially common in young children with vertical hearts rotated in a clockwise direction. In a few instances an inverted T without a Q wave was observed at V_4, indicating that the electrode was probably not over the left ventricle.

Widening of QRS complexes and depressed S-T segments with inverted T waves were not observed in any of the 44 rheumatic children or adolescents with organic heart disease. These changes, diagnostic of left ventricular hypertrophy in adults, are most frequently associated with degenerative diseases, such as hypertension and arteriosclerosis, and, therefore, are uncommon in young persons.

The tracings of the unipolar precordial leads of children with organic heart disease and cardiac enlargement were compared with those of rheumatic children with normal cardiac findings. Irrespective of the electrical position of the heart, a definite difference in pattern was observed. The tracings of children with organic heart disease, in most instances, showed small R and deep S waves in leads facing the epicardium of the right ventricle and tall R waves in leads facing the left ventricle. This pattern was observed in children with mitral stenosis, as well as in those who had aortic involvement or mitral insufficiency without stenosis. A pattern indicative of right ventricular hypertrophy was seen in only one instance, in a boy with mitral stenosis and a long-standing history of rheumatic fever. The precordial leads of the 87 children classified as having potential and possible rheumatic heart disease showed no evidence of either left or right ventricular hypertrophy.

11. Master, A. M.: The Electrocardiogram and X-Ray Configuration of the Heart, ed. 2, Philadelphia, Lea & Febiger, 1942.

As a means of obtaining further evidence of left ventricular hypertrophy, the voltage of the R wave in the augmented unipolar limb leads was studied. In the group with organic heart disease and cardiac enlargement, high voltage at aV_F was frequently observed in subjects with electrically vertical hearts. In children with horizontal hearts, on the other hand, high voltage in aV_L was observed in only a single instance. It was our impression that the failure to demonstrate high voltage in the augmented unipolar limb leads with equal frequency in patients with horizontal as in those with vertical hearts might be related to the position of the left ventricle in the thorax and was probably not due to a lesser degree of hypertrophy.

First and his co-workers studied unipolar precordial leads in rheumatic subjects.[12] They reported that, even in patients with mitral stenosis, the predominant precordial pattern was that of left rather than of right ventricular hypertrophy. Although our observations are similar, in our opinion further studies of normal, as well as of rheumatic, children are needed before the pattern of the precordial leads without other changes should be accepted as definite evidence of left ventricular hypertrophy. At present adequate information on the effect of the proximity of the heart to the wall of the chest and of variations in rotation on voltage at different sites over the precordium is not available.

CONCLUSIONS

1. The value of standard, augmented unipolar limb and precordial electrocardiograms as a means of determining cardiac hypertrophy was studied in 156 children and adolescents in the quiescent stage of rheumatic fever.

2. A P wave of 0.10 second or more in the standard leads is a useful indication of auricular hypertrophy. In most instances this sign is correlated with evidence of enlargement of the auricle on roentgenologic examination (esophagram).

3. Augmented unipolar limb leads are of aid in the interpretation of axis deviation.

4. Electrocardiographic evidence of right ventricular hypertrophy is most readily demonstrable by means of unipolar precordial leads, and the condition may occur in the absence of, or concomitant with, left as well as right axis deviation.

5. Definite criteria for the electrocardiographic diagnosis of left ventricular hypertrophy in young persons with rheumatic heart disease have not been established. It seems possible, however, that high

12. First, R. S.; Stickle, A. W., and Bayley, R. H.: Electrocardiographic Studies in Rheumatic Heart Disease with Reference to Interpretation of Multiple Unipolar Precordial Leads, Am. Heart J. **33**:1, 1947.

voltage in the augmented unipolar limb leads accompanied with the pattern of left ventricular hypertrophy in the unipolar precordial leads indicates hypertrophy of the left ventricle. Even in the absence of high voltage in the limb leads, small R and deep S waves in leads facing the epicardium of the right ventricle and tall R waves in leads facing the left ventricle suggest left ventricular hypertrophy.

123 Waverly Place (11).

RESPIRATORY AIR FLOW PATTERNS IN CHILDREN

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AND
LESLIE SILVERMAN, D.Sc.
BOSTON

THE STUDY of respiratory diseases in children is handicapped by technical difficulties encountered in applying standard methods of measuring pulmonary function, particularly in the youngest age group. Even when nose clip and mouth piece are tolerated, the psychologic reaction to interference with natural breathing is likely to destroy the validity of measurements. The air flow recorder (pneumotachograph) of one of us (L. S.) and associates [1] appeared to offer a minimum of disadvantages in application to children. Its use is the basis for this investigation. The chief advantage of pneumotachographic recording, apart from its accuracy, is the imperceptible resistance to breathing. The use of a comfortable anesthesia mask instead of a mouth piece and the small size of the apparatus, which can be kept out of sight of the patient, are additional advantages.

It has been shown that striking deviations from the normal air flow pattern may be demonstrated with the pneumotachograph in adults with asthma,[1] advanced silicosis [2] and tuberculosis.[3] In the pediatric age group, there are large numbers of patients with severe chronic or recurrent respiratory disease. This study was undertaken for the purpose of determining the diagnostic and prognostic value of pneumotachographic tracings in children with a variety of pathologic conditions affecting the respiratory system.

Aided by a grant from the National Foundation for Infantile Paralysis.

From the Departments of Physiology and Industrial Hygiene of the Harvard School of Public Health, and the Medical Services of the Infants' and Children's Hospitals.

1. Silverman, L.; Lee, R. C., and Drinker, C. K.: A New Method for Studying Breathing, with Observations upon Normal and Abnormal Subjects, J. Clin. Investigation **23**:907-913 (Nov.) 1944.

2. Silverman, L.: Respiratory Air Flow Characteristics and Their Relation to Certain Lung Conditions Occurring in Industry, J. Indust. Hyg. & Toxicol. **28**:183-196 (Sept.) 1946.

3. Rao, M. N., and Silverman, L.: Respiratory Patterns in Pulmonary Tuberculosis, Am. Rev. Tuberc. **54**:574-581 (Dec.) 1946.

MATERIAL AND METHODS

The use of the pneumotachograph is illustrated diagrammatically in figure 1 and is explained more fully later. Figure 2 is a side view of the portable model of the pneumotachograph used in obtaining most of the records in the present study.

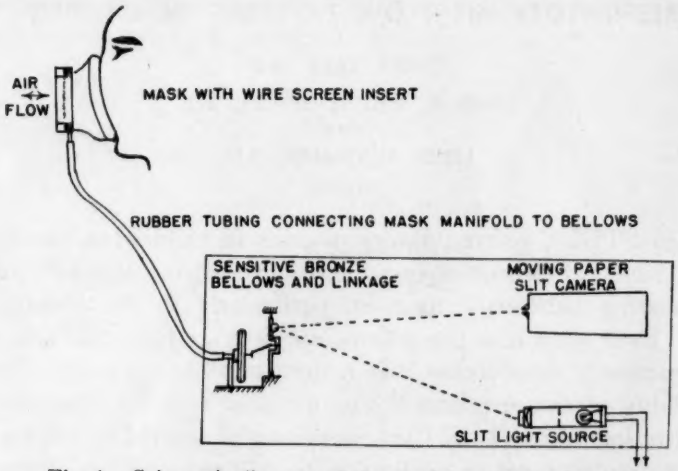

Fig. 1.—Schematic diagram of the air flow recorder in use.

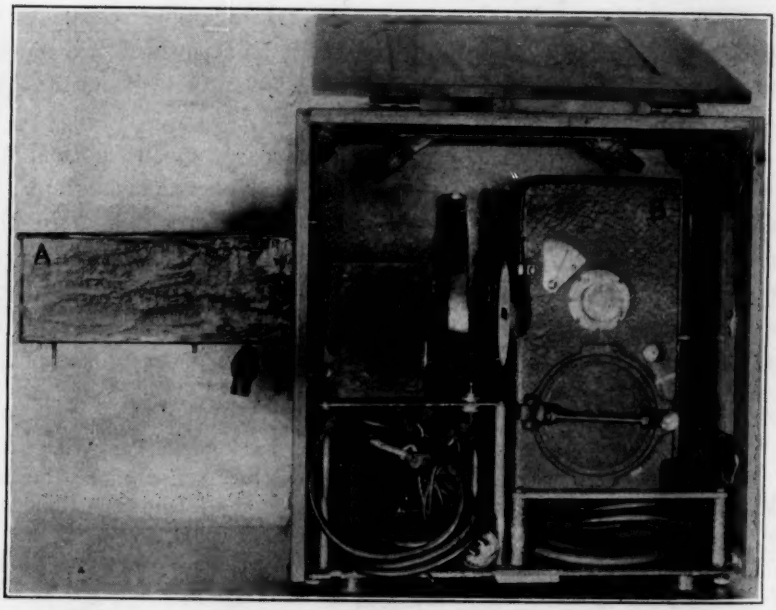

Fig. 2.—Portable pneumotachograph. *A* is the housing of pressure recorder and *B*, a camera of the type used in electrocardiographic machines.

The tracings were obtained with the subject breathing through a plastic anesthesia mask (fig. 3) which was fitted at the orifice with a diaphragm of fine mesh wire screening (400 mesh of an alloy of nickel and copper [monel® metal]).

The interposition of the diaphragm at the orifice of the mask resulted in a slight impedance to the free flow of the respired air. As a result, there was a small variation of the pressure within the mask during the respiratory cycle—above atmospheric pressure in expiration and below in inspiration. The magnitude of the fluctuations in intramask pressure was small (2.5 mm. of water at a flow rate of 100 liters per minute, with a screen 1.6 inches [4.06 cm.] in diameter).[2] The subject was unaware of any obstruction to respiration. The

Fig. 3.—Modified face mask. *A* is the diaphragm of 400 mesh wire screen and *B*, the side tap.

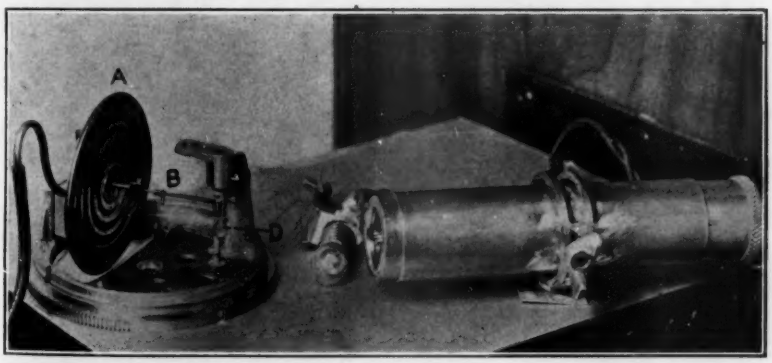

Fig. 4.—Assembly of the bellows linkage and mirror. *A* is the wafer bellows, *B*, linkage, *C*, helical spring and *D*, mirror mounted on pivot.

pressure changes in the mask which accompanied respiration were transmitted through a manifold to a side tap just proximal to the diaphragm. Rubber tubing connected the tap to a sensitive wafer bellows of phosphor bronze● which responded linearly to the pressure changes within the mask (figs. 1 and 4). Movements of the bellows were transmitted by means of a metal linkage to a pivot with a helical restraining spring. A small mirror was mounted on the pivot shaft. A narrow, vertical beam of light was focused on the mirror and reflected

through the slit of a constant speed camera of the type used in standard electrocardiographic machines. In response to the pressure fluctuations in the mask which accompanied respiration, the light beam was displaced horizontally. These excursions about the resting position were converted into diphasic waves by

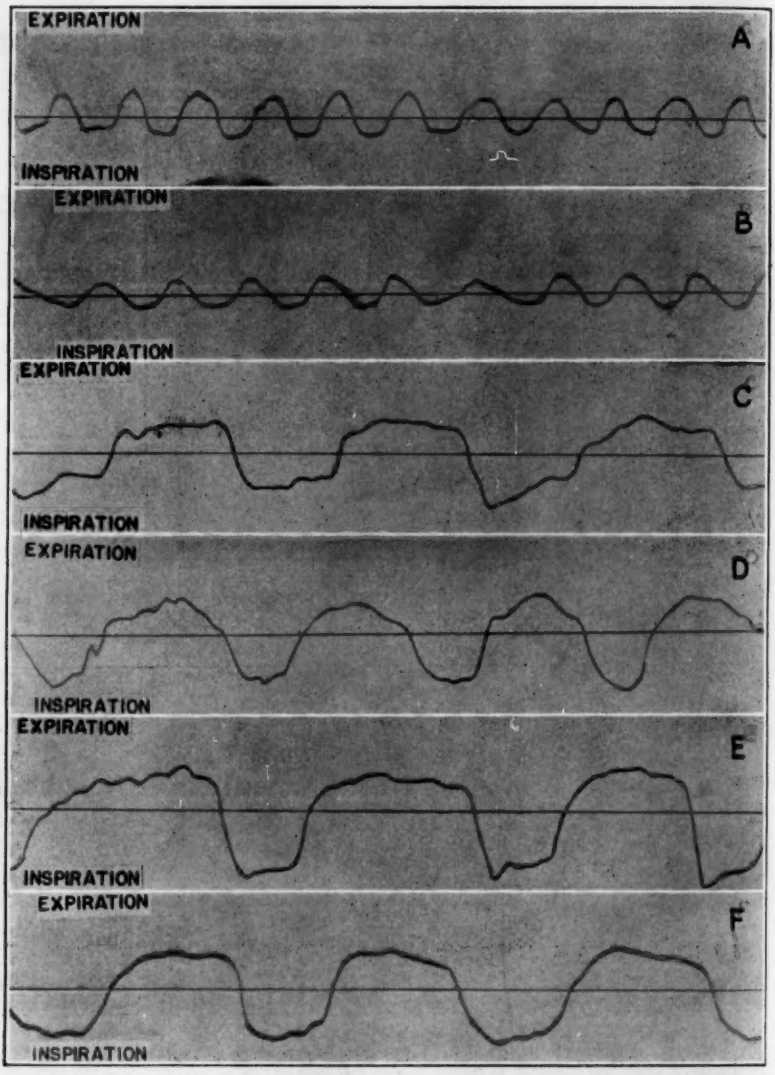

Fig. 5.—Normal tracings. Expiration is indicated above base line, inspiration below. Tracing *A* is of a 3 day old infant, *B*, of a 7 week old infant, *C*, of a 5 year old child, *D*, of an 8 year old child, *E*, of a 10 year old child and *F*, of a 30 year old adult.

movement of the film at right angles to the path of the light beam. A mechanical timer was incorporated in the apparatus.

The response of the recording system was linear to the rate of air flow up to 120 liters per minute with a 2 inch (5.08 cm.) screen. Above this, the departure

from linearity was about 5 per cent up to flow rates of 200 liters per minute. The tracings obtained recorded the variations in the instantaneous rate of air flow throughout the respiratory cycle with a lag of the order of 0.01 second. The tidal air and respiratory minute volume could be determined by planimetric integration of the respiratory air flow curve. Additional data, such as peak rates of flow in inspiration and expiration and the duration of the phases of the respiratory cycle, could also be obtained from the records.

The apparatus can be readily calibrated if quantitative ventilatory measurements are desired. The mask assembly is attached by rubber tubing to a flowmeter of the rotameter type. By means of a vacuum pump, air is drawn through the flowmeter and diaphragm at varynig rates. The side tap proximal to the diaphragm is connected to the recording element of the pneumotachograph. The deflection of the light beam from its zero position is photographed at varying known rates as determined by the flowmeter.

Diaphragms of different diameters were used. The pressure change within the mask at a given air flow is inversely proportional to the area of the diaphragm, as a smaller screen constitutes a greater obstruction to air flow. Four screen diameters were adequate for satisfactory recording of all ranges of ventilation encountered in infants, children and adults.

Most of the records were taken with the subject in the supine position and the remainder in the sitting posture. There was no significant difference in the shape of the air flow curve recorded in the two positions.

In order to determine the characteristics of the normal air flow pattern, records were obtained on 303 normal infants, children and adolescents. Most of these subjects were students of a public school or a boarding school for boys in the vicinity of Boston. About 10 per cent of the group were obtained in the outpatient department of the Children's Hospital of Boston.

The age distribution of the normal subjects was as shown in the tabulation.

Age Group (Years)	Number of Subjects
Under 2	7
2 to 3	4
4 to 5	21
6 to 9	65
10 to 14	71
15 to 18	135
Total	303

All the patients with respiratory disease were studied in the outpatient department and wards of the Infants' and Children's Hospitals.

RESULTS

Normal Children.—The records in normal children and infants do not differ significantly in contour from the tracings previously reported for normal adults.[1] The subjects ranged in age from 3 days to 18 years. The tracings in figure 5 illustrate the characteristics of the normal respiratory air flow pattern in infants, children and adults. In all the figures, expiration is above the base line and inspiration is below. The rise and fall of the curve above the base line signifies a rise and fall in the rate of expiratory air flow. The curve returns to the base line of zero flow, and then rises and falls in inspiration with the corresponding changes in the rate of inspiratory air flow. There are obvious

variations in contour in successive respiratory cycles. Superimposed on the phasic variations of inspiration and expiration are oscillations of small amplitude. The significance of the oscillations is not known, but they are absent in many abnormal tracings. In some instances fluctuations in air flow due to cardiac activity appear on the record. The curve in inspiration is roughly "U" shaped. In expiration, the

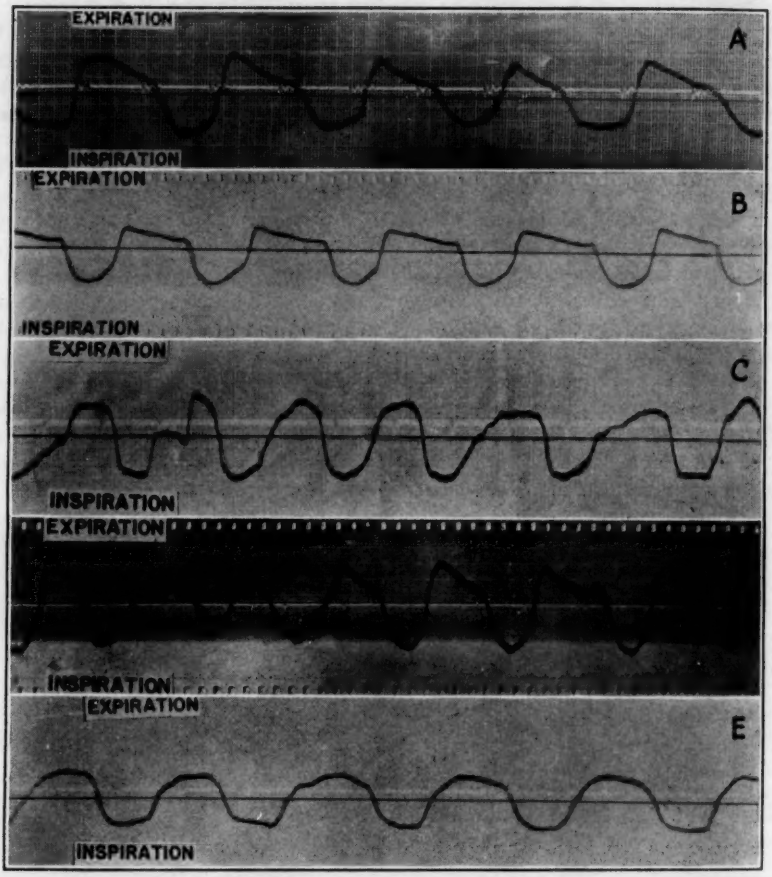

Fig. 6.—Tracings of subjects with intrinsic pulmonary disease. Tracing *A* was made during silicosis, moderately advanced in an adult patient, *B*, during emphysema in an adult, *C*, during acute lobar pneumonia in a 6 year old boy, *D*, during severe bronchiectasis in a 9 year old boy and *E*, during abscess of the upper lobe of the left lung in a 9 year old boy.

convexity is upward, and flow rates close to the maximum are maintained during the major portion of the expiratory phase. There is a smooth, uninterrupted transition from expiratory to inspiratory air flow. Records *A* and *B* in figure 5 were obtained from a 3 day and a 7 week old infant, respectively. The minor differences between these

tracings and those of older subjects, as illustrated by the remaining records in figure 5, are probably caused by the more rapid rate of respiration, which tends to diminish the normal irregularities of flow.

Intrinsic Pulmonary Disease.—Abnormal air flow patterns of a rather uniform type were obtained in patients with a variety of diseases affecting the lungs. This pattern has been described previously in adults with advanced silicosis, emphysema, asthma and extensive fibrosis secondary to pulmonary tuberculosis. In children, the same pattern was found in subjects with asthma, bronchiectasis, kyphoscoliosis and severe pulmonary disease associated with fibrosis of the pancreas.

Figure 6 *A* was obtained from an adult with moderately advanced silicosis and illustrates this type of abnormal pattern. The peak air

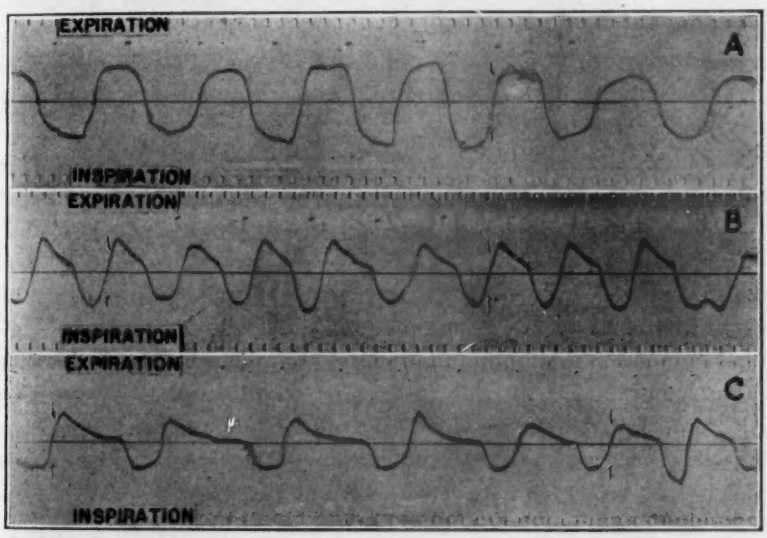

Fig. 7.—Tracings of subjects with pulmonary disease associated with pancreatic fibrosis. *A* is of a child 3 years of age with normal physical findings and mild roentgenographic changes. *B* is of a child 3 years of age with dyspnea, rales, emphysema and roentgenographic signs of patchy atelectasis and emphysema. *C* is of a child 5 years of age whose physical and roentgenologic findings were similar to those of the patient of tracing B.

flow rate in expiration (above the base line) is reached early and then declines almost at once. In the normal picture, a rate of flow close to the maximum is sustained through about 60 per cent of expiration and imparts a dome-shaped configuration to the expiratory curve. The expiratory curve in the aforementioned pulmonary diseases is often concave in its descending limb. The oscillations which are superimposed on the phasic variations of flow in the normal are lost in both inspiration and expiration in the abnormal tracing. In addition, the normal minor variation in contour of successive respiratory cycles

practically disappears. This gives the record a stereotyped and mechanical configuration. Attempts to reproduce this pattern voluntarily in normal subjects did not succeed.

Figure 6*B* was obtained from an adult patient with emphysema and is similar to 6*A*, differing only by having a straight-line decrease in expiratory flow instead of a concave curve.

All records obtained on patients with acute inflammatory conditions of the lung were normal. Figure 6*C* illustrates a record from a 6 year old boy moderately ill with an attack of acute lobar pneumonia involving the upper lobe of the right lung. The pattern differs in no way from that of normal subjects. On the other hand, a 9 year old boy with extensive bronchiectasis yielded a definitely abnormal air flow pattern (fig. 6*D*). Subacute or chronic pulmonary infections in children were not characterized by abnormal tracings, unless the process was severe and diffuse. Figure 6*E* illustrates a normal tracing obtained from a 9 year old boy moderately ill with an abscess localized to the upper lobe of the left lung.

It is likely that an abnormal pneumotachograph tracing in a patient with pulmonary infection indicates the presence of severe and extensive disease.

Pulmonary Disease Associated with Pancreatic Fibrosis: In figure 7 are illustrated three tracings obtained in a group of patients with pancreatic fibrosis proved by analysis of duodenal enzymes.[4] The patients ranged in age from 2 to 8 years. In all the children, abnormalities were detectable by roentgenographic examination. Two patients, aged 2 and 3 years, respectively, had mild roentgenologic changes and normal findings on physical examination of the lungs. The pneumotachogram of the latter patient was normal (fig. 7*A*).

Two patients, aged 3 and 5 years, had well marked evidence of this condition, i. e., dyspnea, rales, emphysema and roentgenologic findings of patchy atelectasis and emphysema. Both of these children had clearly abnormal pneumotachograms (fig. 7*B* and *C*). Two other subjects, aged 6 and 8 years, in whom the findings were of intermediate severity, had tracings which were within normal limits. The occurrence of an abnormal respiratory air flow pattern in patients with this disease probably indicates the presence of severe and diffuse pulmonary involvement.

Asthma: Tracings were obtained of 6 children during asthmatic attacks; each of these was abnormal. The group ranged in age from 9 months to 9 years. Figure 8*B*, *C* and *D* are records obtained, during an attack, of 3 patients, aged 5 years, 9 months and 8 years, respectively. Figure 8*A* illustrates the normal tracing of the 5 year old child

4. Dr. Charles May gave permission for observation of these patients.

taken during an asymptomatic interval. The records during asthmatic episodes are qualitatively identical in pattern. They all show rapidly attained and poorly maintained expiratory air flow, i. e., decline in velocity shortly after peak flow is reached, loss of the oscillations which are normally superimposed on the phasic variations and a high degree of uniformity in the pattern of successive respiratory cycles. The variability in the appearance of the tracings obtained from the different asthmatic patients is a reflection of quantitative variations in rate of

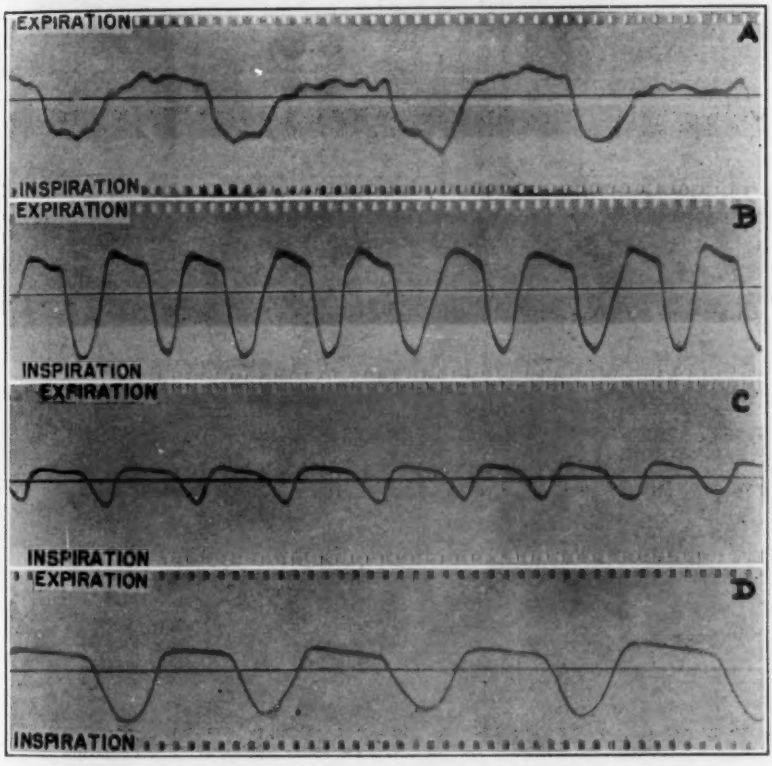

Fig. 8.—Tracings of children with asthma. *A* was made on a child 5 years of age during an asymptomatic interval. *B* is of the same patient as tracing *A* during a severe asthmatic attack. *C* is of an infant, 9 months old, during an asthmatic attack, and *D* is of a child 8 years of age also during an asthmatic attack.

respiration, velocity of flow, the duration of the phases of the respiratory cycle and variations in recording apparatus.

Records of 13 other persons with a history of asthma which were taken at asymptomatic periods were normal. It was previously shown that pneumotachograph recordings of adults with the pulmonary complications of chronic asthma show an abnormal pneumotachographic pattern at times when there is no evidence of active asthma. The

reversibility of the air flow alteration in children, illustrated in figure 8 *A* and *B*, is striking. The emphysema tracing in figure 6 *B* was obtained from an adult patient with long-standing asthma. In this patient the pneumotachographic abnormality was constant and was not altered by the clearing of superimposed asthmatic episodes.

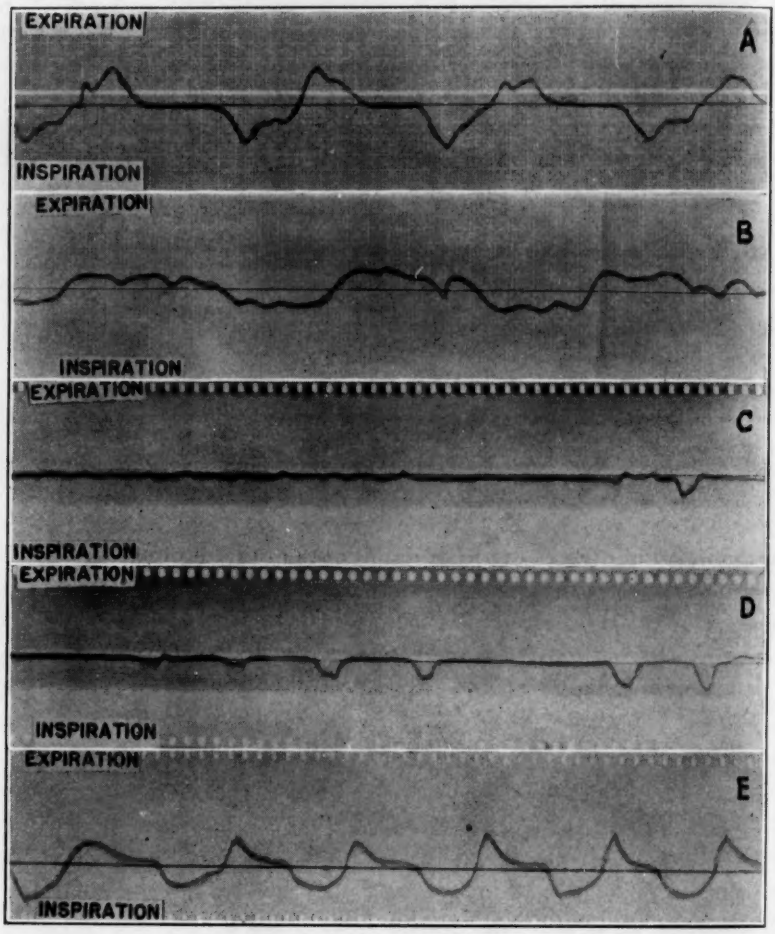

Fig. 9.—Ventilatory disorders of extrapulmonary origin. Tracing *A* is of a child 5 years of age with deformity of the chest resulting from dyschondroplasia, *B*, of an adult with diaphragmatic tic, *C*, of an infant, 4 months old, with severe laryngotracheobronchitis, when the tracheotomy tube was open and the mask applied to the face, *D*, of the same patient as in tracing *C*, when the tracheotomy tube was closed and the mask applied to face, and *E*, of a child, 8 years old, with severe kyphoscoliosis.

Ventilatory Disorders of Extrapulmonary Origin.—In this group, the respiratory dysfunction is primarily mechanical. The tracing in figure 9 *A* was obtained from a 5 year old boy with severe dyschondro-

plasia. The chest of this child was severely flattened bilaterally, and there was also a prominent pigeon breast deformity. The thorax was almost entirely fixed and moved little with respiration. The restriction in volume of the thorax resulted in a downward displacement of the liver to a position almost entirely below the costal margins. The vital capacity of this child was only 320 cc. Respiration was accomplished solely by diaphragmatic movement. The pneumotachogram of this patient is strikingly abnormal in that there is a complete cessation of air flow at the end of expiraton in each respiratory cycle. This pattern of breathing was also observed in patients with severe paralysis of the intercostal muscles resulting from poliomyelitis. The chest of this patient can be considered functionally paralyzed because of the association of extreme diminution in volume with thoracic fixation.

Figure 9 *B* illustrates an unusual pattern of breathing in an adult female patient with recurrent attacks of diaphragmatic tic. These episodes are characterized by rapid, involuntary contractions of the diaphragm occurring at the rate of six to ten times in each respiratory cycle. The seizures adversely affect the efficiency of the patient's respiration. The spasmodic contractions are visible on the lower lateral aspects of the thorax. In the pneumotachogram, they appear as repetitive dips in the air flow tracing.

Figure 9 *C* and *D* shows the air flow patterns of a 4 month old infant who had a tracheotomy to relieve obstruction caused by laryngotracheobronchitis. The records were obtained with the mask applied to the face. It can be seen in figure 9 *C* that with the tracheotomy tube open there was almost no air flow through the nose and mouth. The tracing in figure 9 *D* was taken with the tracheotomy tube occluded. There was a progressive increase in the volume of inspiratory flow but almost no expiratory flow during the fifteen second interval during which the tube was closed.

Pneumotachograms were obtained from 8 children with severe kyphoscoliosis; in only 1 child was the pneumotachogram abnormal (fig. 9 *E*). The air flow pattern resembled that described for silicosis and asthma.

Abnormalities of Ventilation Due to Poliomyelitis: Records of respiratory air flow were obtained with the pneumotachograph of 59 patients with poliomyelitis. Of this group, 87.0 per cent (51) were children 14 years of age or younger. The ages of the patients ranged from 14 months to 33 years. In 53 patients, records were obtained in the first two weeks of their illness, and in most of them during the first week. Another group of 6 patients was studied eight to twenty months after the onset of respiratory muscle weakness following an attack of poliomyelitis. Seven of the 59 patients yielded definitely

abnormal tracings, and all these showed clinical evidence of weakness of the respiratory musculature. Five of the 7 patients with pneumotachographic abnormalities were treated in mechanical respirators for periods of several days to eight months. All the patients with abnormal pneumotachograms had weakness of the intercostal muscles, and 5 had diaphragmatic weakness as well. In 3 patients with paralysis of

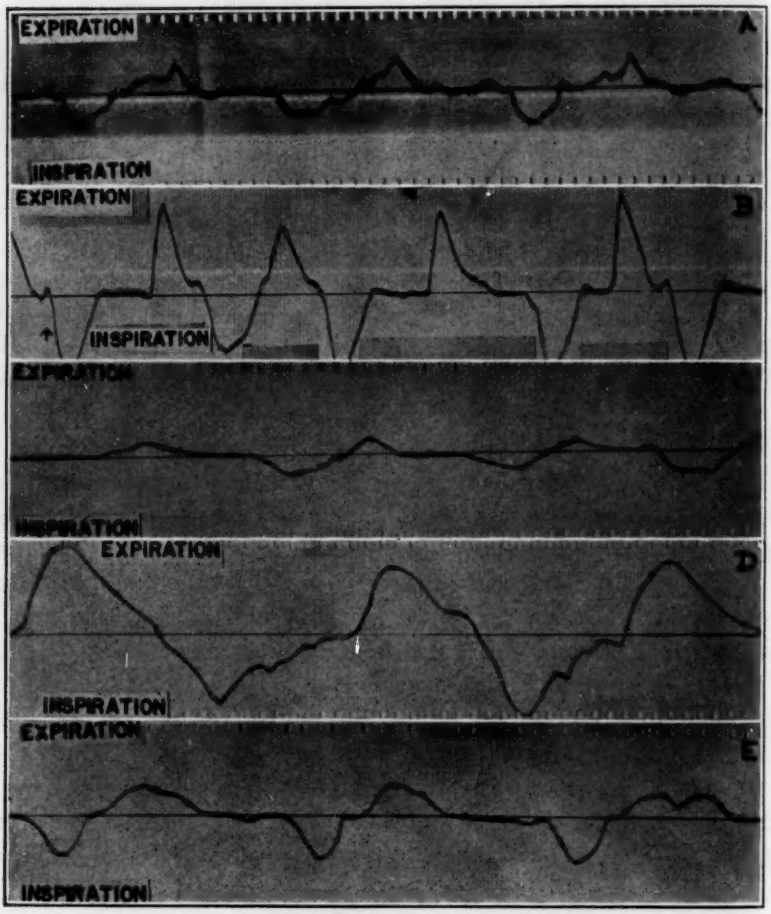

Fig. 10.—Abnormalities of ventilation due to poliomyelitis. Tracing *A* is of a girl 14 years of age with severe diaphragmatic paralysis and moderate paralysis of the intercostal muscles, *B*, of a woman 26 years of age with weakness of the diaphragm and intercostal muscles, *C*, of a boy 7 years of age with slight weakness of diaphragm and moderate paralysis of intercostal muscles, *D*, of the same patient as in tracing *C* during voluntary hyperventilation, and *E*, of a girl 8 years of age with moderate intercostal weakness and severe paralysis of the left side of the diaphragm.

cranial nerves and cerebral symptoms who did not have weakness of respiratory muscles, the interpretation of unusual records was equi-

vocal because the pattern of breathing could have been produced by excitement or sedation. Of 3 other patients with bulbar signs, 2 had normal records and 1 had almost total paralysis of the extremities and respiratory muscles in addition to the involvement of cranial nerves.

Ten patients, or 17 per cent of the entire group, showed clinical evidence of paralysis of respiratory muscles. The high incidence of respiratory complications is the result of the inclusion of 6 patients who were so severely affected as to be still under hospital treatment eight to twenty months after onset of their illness. Seven of the 10 patients with clinically detectable weakness of respiratory muscles had abnormal tracings. Three of these were in the group with acute illness, and 4 were in the late group. The 1 acutely ill patient with a normal pneumotachograph and involvement of respiratory muscles had only slight weakness of the left side of the chest. This was manifested on deep breathing only and caused no ventilatory embarrassment. Two patients in the convalescent group had normal pneumotachographs in the presence of slight weakness of the intercostal muscles on one side in one and minimal residual diaphragmatic paralysis in the other. One patient in the acute stages of illness manifested an abnormal air flow pattern with minimal intercostal weakness (fig. 11 *A*). The impairment of the thoracic musculature in this patient was evident only during a voluntary deep inspiration. This showed itself as a cephalad elevation of the sternum without an increase in anteroposterior diameter of the chest. Two of the patients were completely dependent on the respirator at the time when the tracings were taken.

The abnormality in the pattern of air flow resulting from paralysis of intercostal muscles is illustrated in figures 10 *A, B, C* and *E* and 11 *A* and *C*. It consists of cessation of air flow at the end of expiration. The period of interrupted air flow approximates the duration of inspiration or expiration and appears as an integral part of the respiratory cycle in successive breaths. One patient who became distressed in a few minutes out of the respirator showed periods of respiratory pause before and after expiration (fig. 10 *B*). This may be a manifestation of a severer impairment because the latter patient exhibited the greatest ventilatory disability of the group, except for 1 patient who had no respiratory movements without the respirator (fig. 11 *D* and *E*).

A further characteristic of these curves is that the contour of expiration resembles an inverted "V." This differs from the normal expiratory curve in which flow rates approaching the maximum are maintained during the greater part of expiration, giving the expiratory curve a more rounded contour.

The appearance of a pause in the respiratory cycle is not the result of therapy in a mechanical respirator. Two of the patients were not

treated in a respirator (fig. 11 *A* and *C*). The presence of the interruption in air flow is indicative of intercostal rather than diaphragmatic paralysis. A patient with complete diaphragmatic paralysis not

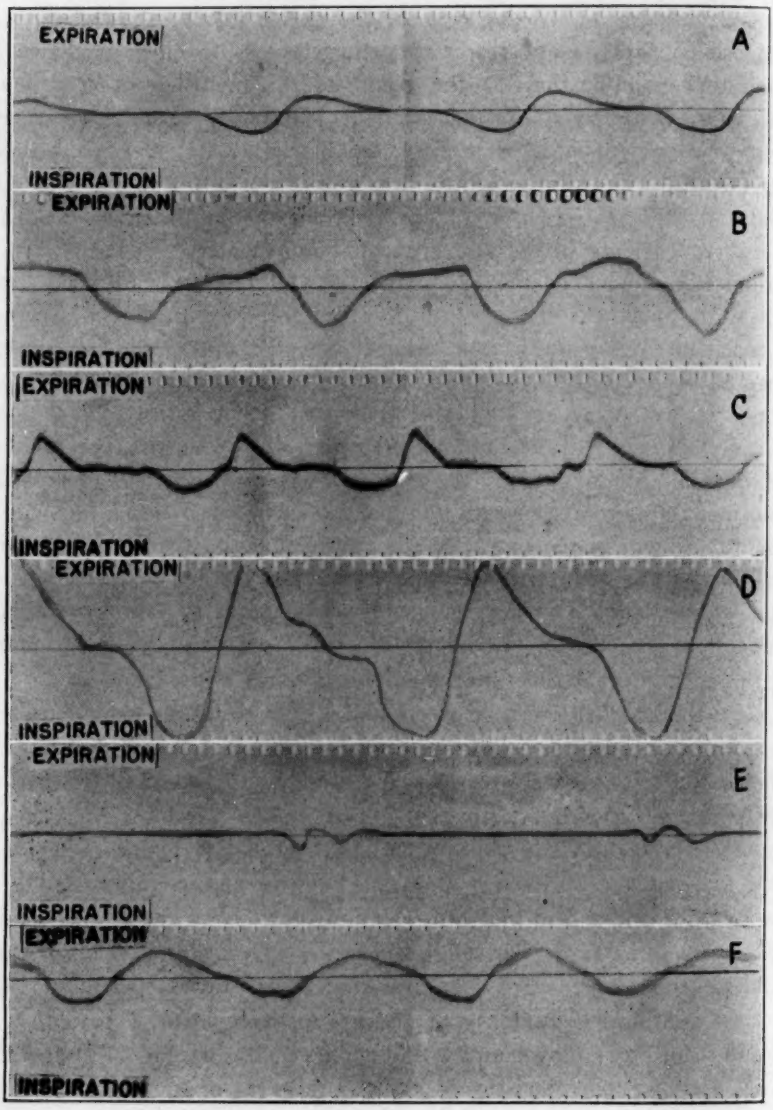

Fig. 11.—Additional tracings of abnormalities of ventilation due to poliomyelitis. Tracing *A* is of a boy 4 years of age with minimal weakness of intercostal muscles on the seventh day of illness, *B*, of the same patient as in tracing *A*, one month later when respiratory muscles were normal, *C*, of a man 26 years of age with moderate paralysis of intercostal muscles, *D*, of an adult, aged 33 years, with complete paralysis of respiratory muscles; the record was taken with the patient in the respirator under negative pressure only, E. of the same patient as in tracing *D* when the respirator was not operating and *F*, of a girl, aged 8 years, with complete paralysis of the diaphragm, not caused by poliomyelitis.

due to poliomyelitis yielded a normal pneumotachogram (fig. 11 *F*). It is interesting that the abnormal tracing illustrated in figure 11 *C* was obtained at a time when the clinical evidence of intercostal paralysis was slight. It was not until three days later with progress of the paralysis that treatment in a respirator was seriously considered.

Attempts to reproduce, in normal persons, the respiratory pattern of intercostal paralysis by binding the chest were not successful. Complete immobilization of the thorax was not accomplished in these experiments.

The tracing of the patient with complete respiratory paralysis is illustrated in figure 11 *D*. The prolonged apnea which appeared when the respirator was turned off is shown in figure 11 *E*. Figure 11 *D* represents the air flow pattern of this patient treated in a mechanical respirator by inspiratory negative pressure alone. The curve of expiration, which is completely passive, fails to show the normally well maintained peak expiratory flow. This is evidence that normal expiration is not entirely passive.

COMMENT

A beginning has been made in a study of the applications and limitations of the pneumotachograph in the investigation of respiratory diseases in children. Abnormality of the lungs must be fairly extensive before pneumotachographic changes appear. Furthermore, alterations in the pneumotachogram are nonspecific, with a variety of pulmonary disorders yielding similar patterns. Asthma was the most consistent disease studied, in that asthmatic attacks invariably produced characteristic changes in air flow pattern.

There are several other limitations to the usefulness of this method as a clinical tool. As might be expected, children under 3 or 4 years are usually frightened by having a mask placed over the mouth and nose, and few satisfactory tracings were obtained in this age group. While quantitative measurements of respiration can be obtained with the apparatus, the requisite calculations are tedious and time consuming.

In the case of patients treated in respirators, there is a good deal to recommend the use of the pneumotachograph for obtaining measurements of minute volume. There is less danger of cross infection with the pneumotachograph mask, which can be cleaned and aired. Application of the mask to the patient's face while the respirator is in use is simple and obviates the necessity of using more cumbersome apparatus. Another advantageous feature is the extremely low resistance to breathing which the pneumotachograph affords.

It is not possible, at this time, to elucidate the mechanism by which such conditions as asthma, bronchiectasis, emphysema, silicosis, advanced tuberculosis and kyphoscoliosis alter the pneumotachogram

in the same fashion. Hyperventilation alone does not simulate this respiratory pattern; breathing against a resistance of 1 mm. of water per liter of air flow results in damping of the curve but does not duplicate the pattern in asthma.

The pneumotachogram may prove useful in establishing a diagnosis of asthma in patients with recurrent pulmonary episodes who have no abnormal pulmonary findings between the attacks. The conversion of the asthmatic pattern to the normal provides an objective demonstration of the efficacy of treatment.

Acute inflammatory disorders of the lungs have not yielded abnormal pneumotachographic findings. With the exception of asthmatic persons, the abnormal tracings occurred only in patients with widespread long-standing parenchymal damage and did not revert to normal in subsequent records. In patients with acute, severe respiratory illness, an abnormal pneumotachogram suggests that there is underlying pulmonary disease which probably antedates the present illness. The possibility remains that the failure to obtain abnormal pneumotachograms in patients with acute pulmonary inflammatory disorders is a manifestation of a less widespread involvement in the patients studied, and not of a more fundamental difference. It has not been conclusively demonstrated whether or not there is any difference between the air flow patterns of patients with acute and with chronic pulmonary processes of equal severity. A study is in progress which should permit correlation of pneumotachographic findings with the degree of pulmonary disability as measured by other tests.

The change in respiratory pattern observed in patients with poliomyelitis was seen in a patient with only one other condition, namely, dyschondroplasia (fig. 9*A*). The compression and fixation of the thorax in this child was nearly sufficient to immobilize it and to place almost the entire burden of ventilation on the diaphragm. The pause in air flow noted in subjects with paralysis of intercostal muscles is not the result of fixation of the thorax by ankylosis secondary to immobilization. This is clear from the fact that it has been observed in patients in the early days of the disease (fig. 11 *A* and *C*). When the abnormal air flow pattern persists months after onset of respiratory paralysis, it may be abolished by hyperventilation. This is illustrated in figure 10 *D*, which is from the same patient as the records shown in figure 10 *B* and *C*. The pause in air flow in the portion of the tracing reproduced here is not present in the first two respiratory cycles but reappears in the third. This may be a manifestation of fatigue of the respiratory muscles. The pneumotachographic abnormality associated with paralysis of intercostal muscles can disappear with improvement in the function of the affected muscles. The tracings in figure 11 *A*

and *B* were taken on the same person one month apart, and the second tracing is normal.

SUMMARY

1. The air flow pattern of normal children obtained with the pneumotachograph is described.

2. A clearcut alteration in the pattern of respiratory air flow was observed in children with asthma, severe bronchiectasis, kyphoscoliosis and the pulmonary disease associated with fibrosis of the pancreas.

3. The abnormal pattern is similar in these conditions and is like that observed in adults with silicosis, emphysema, asthma and extensive fibrosis secondary to pulmonary tuberculosis.

4. A decided alteration from the normal pneumotachogram was seen in 6 patients with paralysis of intercostal muscles resulting from poliomyelitis.

5. The uses and the limitations of the pneumotachograph are discussed.

55 Shattuck Street (15).

Case Reports

MICROCEPHALIA AS A COMPLICATION OF PNEUMOCOCCIC MENINGITIS

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AND
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SAN FRANCISCO

WITH THE advent of chemotherapy and subsequent recovery from a disease formerly 100 per cent fatal, hitherto unsuspected complications can be anticipated. The following case of microcephalia resulting from pneumococcic meningitis is therefore reported.

REPORT OF A CASE

S. N., a 2½ month old white girl, was admitted to Children's Hospital on March 19, 1946 with the presenting complaint of irritability, rigidity and pallor of seven hours' duration. Following her 3 a. m. feeding on the day of entry, the patient was noted to become listless, irritable and, then, semicomatose. She was seen by one of us (H. E. T.), who observed generalized twitching, bulging fontanel and semicomatose state. The temperature was 102 F. rectally. The patient was hospitalized immediately. On her admission respirations numbered 40 to 60 per minute. The lungs, however, were clear to percussion and auscultation. The heart rate was 170 with a tick-tack rhythm. Kernig's reflex was present bilaterally. The extremities were held in a semirigid position. The reflexes were all hyperactive.

Spinal puncture revealed cloudy fluid, with 180 cells per cubic millimeter, of which 92 per cent were polymorphonuclear forms. The cloudiness was due largely to an abundance of organisms, the direct smear being filled with pneumococci identified as type B4. On her entry the patient's hemoglobin concentration was 10.7 Gm. Red blood cells numbered 3,830,000, white blood cells, 7,800, and polymorphonuclear cells, 47, with 25 per cent nonfilamented forms. The patient was started on penicillin therapy parenterally, 30,000 units every three hours. One gram of sulfadiazine was given parenterally; fluids and plasma were administered intravenously. The patient was given oxygen continuously because of cyanosis and labored respiration. By 11 p. m. on the evening of entry, the patient's general condition had improved; respirations were slower, and there was less cyanosis. Parenteral administration of penicillin was continued; sulfadiazine was given orally, and two doses of 5,000 units each of penicillin were given intrathecally on successive days. Until March 22, the patient's general condition improved. The temperature ranged between 99.6 and 101.2 F. The fontanel remained full.

At 9 p. m., March 22, the temperature rose to 101.2 F. The patient had a convulsive seizure, mainly on the left side. The respirations were rapid and labored. Abdominal distention was present. The child was placed in oxygen, and the convulsive seizures were controlled with barbiturates, only to recur about two hours later. On the following day, convulsions again occurred. The eyes deviated to the left, and the right side became rigid. The spinal puncture at this time was performed with difficulty ,and blood-stained fluid was obtained. There was no increase

From the Children's Hospital.

in pressure. The cultures were negative for pathogenic organisms. On March 24 it was first noted that the anterior fontanel was sunken. The temperature dropped to 94.4 F. During this time the sulfadiazine level was maintained at about 19 mg. per hundred cubic centimeters by parenteral administration, and a transfusion was given.

On March 25 the spinal fluid which was drawn clotted promptly. There were no organisms present on direct examination, and no growth occurred in four days. A second spinal puncture on March 27 was unsuccessful, and another puncture on March 29 revealed fluid which again clotted almost immediately. Thirty-four cells remained in the unclotted portion of the fluid. The cultures were negative for organisms. The fontanel continued sunken in spite of parenteral administration of fluids in adequate amounts. It was felt that the sunken fontanel, the difficulty in obtaining spinal fluid by tap and the clotting of the fluid obtained were consistent findings, indicating an unusual process occurring within the central nervous system. On March 30 it was noted that the fontanel seemed to be overlapped by the parietal bones. On April 4 parenteral and oral therapy were discontinued. The spinal fluid showed 34 cells, and cultures remained negative for organisms. On April 7 the fontanel still showed overriding of the sutures. The patient gradually improved but did not regain consciousness.

The patient was dismissed to care at home on April 15. She ate well and gained weight. At times she showed some slight degree of spasticity. The fontanel remained small and sunken, and there continued to be some overlapping of the parietal bones.

After her dismissal from the hospital, the child was followed in the office. She ate, slept, gained weight and grew rapidly but failed to show any signs of intelligence. At the age of 5 months, in June, 1946, the circumference of her head was 37 cm., and it appeared to be small as compared with the size of her body. The fontanel was almost closed. From then on, the head became obviously microcephalic in appearance. At 7 months the circumference was 39 cm.

On examination July 24, 1947 at the age of 19 months, she weighed 29 pounds (13.2 Kg.) and was 34 inches (117 cm.) long. The circumference of the head was 41 cm.; the circumference of the chest was 49.5 cm. The child was very large for her age, which was a hereditary trait. Her parents and older sister were all large. She was unmistakably microcephalic with the characteristically tapering or pointed head. She was unable to turn over, sit up and functioned only at the minimal level. She was committed to the state institution for subnormal children after this examination.

The patient died at the age of 22 months. The following pathologic report on examination of the head was made by Dr. N. Malamud, pathologist, Langley Porter Clinic-Hospital, San Francisco.

The clinical diagnosis was idiocy and microcephalia (sequelae of pneumococcic meningitis).

Gross Anatomic Report.—The brain weighed 800 Gm. and was moderately reduced in size. The cerebral tissue of the left hemisphere was mechanically macerated, this change apparently resulting from adhesions to the overlying dura. The convolutional pattern in the right hemisphere appeared to be normal. The leptomeninges were delicate throughout. The basal vessels were thin walled. On section, the cerebral cortex for the most part appeared to be of normal width and well demarcated from the white matter, but there were scattered small segments of cortex in which the tissue was pale and undistinguishable from the white matter. Ammon's horns appeared atrophic. The white matter was diffusely reduced and gray, particularly in its central part. The corpus callosum was

somewhat reduced. The lateral ventricles were considerably dilated, more so on the left, and there was a slight shift to the right. On the right side, practically the entire head of the caudate and the anterior portions of the putamen and globus pallidus were destroyed and replaced by a large cyst with irregular walls and a brownish membranous content. A smaller cyst was seen in the left globus pallidus. The thalamus was largely replaced by diffuse white scars obliterating its nuclear structures. The cerebral peduncles were rather narrow as were also the pyramidal tracts through the pons and medulla. There were no other gross changes through these last two structures.

Histologic Report.—The dura and, to some extent, the leptomeninges showed fibrosis with only an occasional lymphocytic and histiocytic cell, the leptomeninges for the most part showing only mild changes. The underlying superficial layer of the cortex showed a well marked marginal gliosis, but the rest of the cerebral

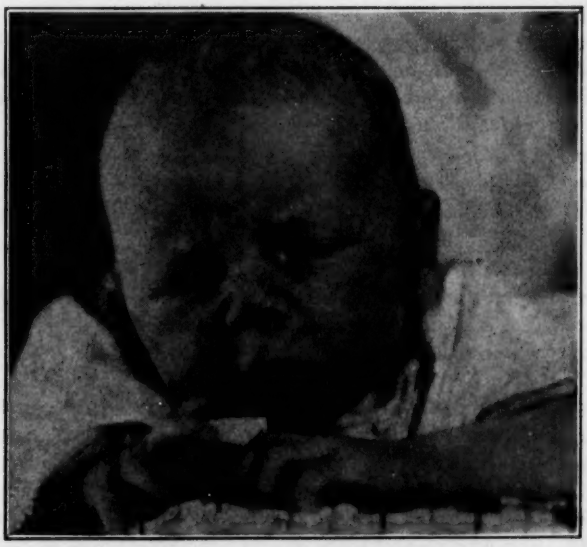

Fig. 1.—Photograph of patient taken at 13 days of age before attack of pneumococcic meningitis.

gray matter was not involved. There were, however, scattered microscopic calcium deposits either in the capillary walls or lying free in the cerebral tissue. The most striking changes were seen in the basal ganglions and in the periventricular regions. Here, cysts lined by irregular walls of gliosis or dense scars enclosing necrotic spaces replaced the subcortical structures and tended to extend irregularly along perivascular spaces of the central white matter. The thalamus showed almost a total degeneration bilaterally and was replaced by dense areas of gliosis and scattered calcium deposits. In some areas, the pattern of the scarring of the basal ganglions and thalami was that of "marble state." The substantia nigra likewise showed extreme degeneration and scarring bilaterally, while the tegmental nucleus and other midbrain structures were more moderately involved.

The interesting pathologic features of this case were the changes in the subcortical ganglions with relatively little residual evidence of the meningitis. Such a complication of purulent meningitis is relatively little known.

The final diagnosis was residual cysts and scars of basal ganglions, thalamus and substantia nigra as a result of meningitis.

COMMENT

This child was normal at birth, as the picture taken when she was 13 days old reveals. Examination at 2½ months likewise showed a normally developed infant, with the head of normal size and shape. The episode immediately following her acute illness characterized by convulsions, sunken fontanel, scant spinal fluid which clotted when collected and the overriding cranial sutures unquestionably represented

Fig. 2.—Photograph of patient taken at 19 months of age showing definite microcephalia as a complication of pneumococcic meningitis.

a pathologic change which retarded the normal development of the brain and eventuated the subsequent microcephalia.

Whether intrathecal therapy contributed to the pathologic development cannot be definitely answered. The infection was extremely severe and occurred in a very young infant. Pneumococcic meningitis with heavy infestation of organisms and lack of cellular response is usually fatal. Recovery with sequelae might therefore be expected.

Experience with other cases also suggests that the disease rather than the therapy may have been the cause of the pathologic change.

In the ward at the same time was a 4 year old child who recovered from influenzal meningitis with evidence of severe cortical damage and amentia. She had had no intrathecal therapy. Another infant treated elsewhere for acute meningitis without intrathecal therapy was observed later to have a small head and low mentality, though the cause and effect were not so apparent.

SUMMARY

A case of severe pneumococcic meningitis in an infant 2½ months old treated with penicillin and sulfadiazine with the disappearance of the organisms and the final clearing of the spinal fluid, but with resultant microcephalia, amentia and death, is reported.

381 Post Street.

MULTIPLE BASAL CELL EPITHELIOMAS IN A FIVE YEAR OLD CHILD

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AND
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NEW YORK

THE OCCURRENCE of several hundred basal cell epitheliomas in a 5 year old child is of sufficient rarity to justify publication. In a group of 1,374 patients with basal cell epitheliomas previously studied at the Memorial Hospital,[1] the average age was 61 years. Sixteen per cent of these neoplasms occurred in subjects more than 75 years old; in fact, 30 per cent of all tumors occurring in persons more than 75 years of age were basal cell epitheliomas. From this fact, it may be inferred that this tumor is the one most commonly seen in aged persons. One often observes the sudden and rapid growth of single hairs in old persons, indicating unusual activity of the hair follicle; a large number of these basal cell epitheliomas in persons more than 75 years of age are of the hair matrix type. Of the 1,374 patients with basal cell epitheliomas, the youngest was 17 years old and only 1.5 per cent were younger than 30 years of age. It has been our experience that squamous cell carcinomas occur more frequently in young subjects than do the basal cell type; e. g., we previously reported 2 instances of squamous cell cancer of the skin in children under 5 years of age.[1]

Under conditions in which the skin is subjected to such irritants as roentgen or strong ultraviolet radiation, basal cell tumors have been seen to develop in the second and third decades of life. We have not seen them in the first decade, however, and this proved case of multiple basal cell epitheliomas of the hair matrix type occurring at the age of 5 years is unusual. The lesions were so numerous that they could not be counted, but a glance at the clinical photograph (fig. 1) reveals that more than 1,000 multicentric foci of basal cell epitheliomas were present in this child.

REPORT OF A CASE

A child 5 years of age was brought by his parents to the Memorial Hospital on Feb. 3, 1943, because of many dark raised spots which first appeared on the anterior wall of the chest and later spread to the axillas and back. Shortly after birth, the infant experienced obvious difficulty with breathing. A diag-

From the Baby Clinic of the Mixed Tumor Service, Memorial Hospital for the Treatment of Cancer and Allied Disease.

1. Pack, G. T., and LeFevre, R. G.: The Age and Sex Distribution and Incidence of Neoplastic Diseases at the Memorial Hospital, New York City, J. Cancer Research **14**:167-294, 1930.

nosis of enlarged thymus was made, and he received roentgen ray therapy four times. The skin over the portal of treatment became red and subsequently persistent brownish tan. Innumerable macular and, later, papular spots had spread to involve not only the skin which was irradiated but also the skin of the back and axillary regions.

The child had had no previous illness except the ordinary contagious diseases.

On physical examination, a well developed, white, blond boy 5 years of age was seen. He had a large skull and widely separated eyes. He showed no abnormalities or deformities. No peripheral adenopathy of significance was present. On the anterior wall of the chest, there was an area, roughly square and about 15 cm. broad and long, which was brownish owing to miliary, papillary pigmented lesions. It was situated in the upper presternal region where radiation over the thymus gland might have been given. The individual lesions were elevated and rather firm. They were not all confined to the area described,

Fig. 1.—Photograph taken at time of first admission to the hospital, showing area of irradiated skin with innumerable pigmented basal cell tumors.

as several more widely scattered lesions occurred extending toward the axilla, on the anterior and medial aspects of the upper arm and on the back and shoulders.

A roentgenogram of the skull revealed considerable enlargement, as in hydrocephalus. The roentgenogram of the chest showed essentially normal findings relative to the lungs.

A tentative clinical diagnosis of papillary pigmented nevi following radiation was made, and it was planned to excise the entire involved region on the anterior wall of the chest by multiple segmented excisions spaced several months apart. In this way, the central portion would be excised at each operation and an interval allowed for stretching of the surrounding normal skin before another segment was removed.

An infection of the upper respiratory tract followed the child's first visit to the clinic, and the first operation was not performed until April 3. A transverse elliptic section about 15 by 7 cm. was removed, the central portion as deep as the pectoralis fascia. Hemostasis was obtained by clamping and

ligature with no. 0 silk suture, and the margins of skin were brought together with similar interrupted sutures. The wound healed per primam, but the child had an elevated temperature for eight days, beginning on the fourth postoperative day, due to pharyngitis and tonsillitis. The histologic pathologic diagnosis was "atrophy of the skin with beginning basal cell epitheliomas."

Between this admission to the hospital and the second one, he had measles and mumps. The second excision was performed on October 13. At this time, a large portion of the remaining lesion was excised, with wider segments at the ends and a narrower one in the center over the sternum. Because of the

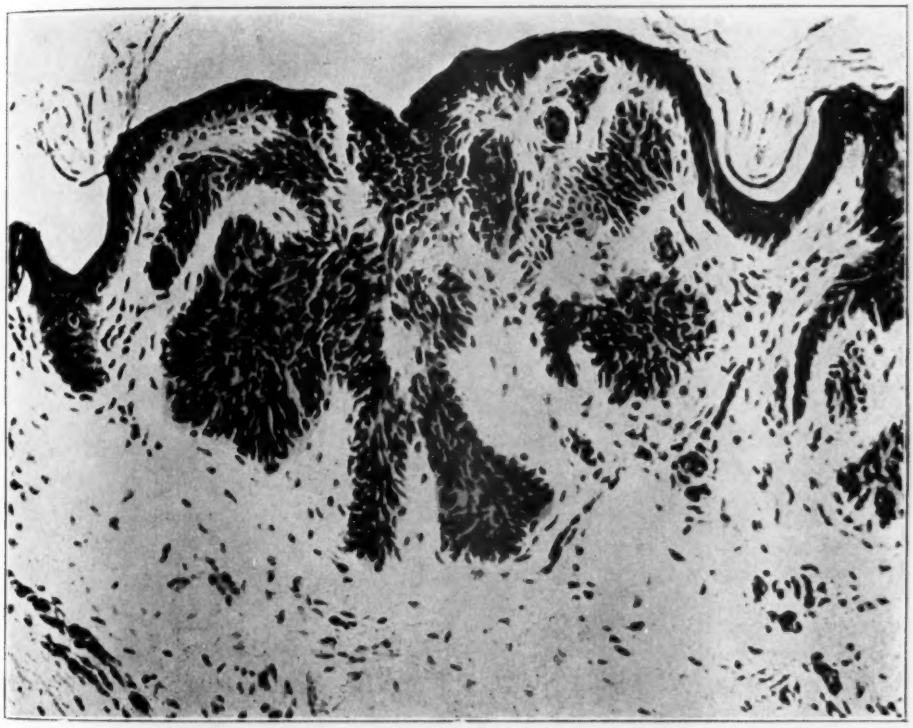

Fig. 2.—Early hair matrix basal cell epithelioma.

previous pathologic report of basal cell epithelioma, two of the lesions on the medial aspect of the left arm were also excised. The pathologic report on examination of the tissue from the wall of the chest was "basal cell epitheliomas and keloidal scar tissue," and that on tissue from the left arm was also "basal cell epitheliomas." To be certain that there had been no confusion of the tissue in the laboratory, another tiny lesion was excised from the left arm before the child was discharged from the hospital. Again the report was "early hair matrix basal cell epithelioma." The wound healed per primam, and the postoperative course was afebrile and uneventful. In the next four months, the scar on the anterior part of the chest developed a definite keloid which was greatly thickened and unsightly. The remaining portion of the original lesion was unchanged.

On May 8, 1944, the third excision was performed, with the removal of the remaining lesion superior to the scar. The pathologic report was, as before, "keloid, with multiple small foci of basal cell epitheliomas, which look rather 'unaggressive.'" There were again an uneventful healing of the wound and postoperative convalescence. One more excission was necessary, as the tension over the sternum prevented wide excisions in this region.

The fourth segmental excision was performed on Feb. 27, 1945, when all of the lesion on the wall of the chest was removed. It had been necessary to leave the central portion of the scar the previous two times; therefore, a wide

Fig. 3.—Photograph taken eleven months after the fourth surgical excision. All the lesions in the area of irradiation were removed, but any treatment of those outside the area was deferred until they showed change or the child could cooperate in order to avoid use of general anesthesia.

keloidal scar over the sternum had resulted rather than the single linear scar which we like to obtain by this technic. The pathologist against reported basal cell epithelioma.

All operations were performed with the patient under general anesthesia.

The child was followed at intervals in the outpatient clinic and had several applications of solid carbon dioxide to the keloid. Otherwise, no further treatment was given. He still had several tiny basal cell epitheliomas on the arms and chest which did not change. He visited the clinic in March 1947, which

was more than four years after his original visit to the Memorial Hospital. Extensive roentgenographic, electrocardiographic and chemical studies were made to determine whether any fibrotic changes in the heart or lungs had occurred. No proof could be obtained of such changes.

The patient was readmitted December 1 in order to check on his progress. There were many scattered lesions from 1 to 3 mm. in diameter on the posterior wall of the chest and the inner aspects of the upper arms, as well as lateral to the excised regions on the anterior wall of the chest. On December 8 about 200 of these were electrodesiccated with the patient under general anesthesia. The wounds healed slowly, and the patient was discharged from the hospital on December 11.

This case is the only one of its type that has been seen in a large tumor clinic for babies, and we feel that it is worthy of the attention of the medical profession.

139 East Thirty-Sixth Street.

CONGENITAL SYPHILITIC NEPHROSIS SUCCESSFULLY TREATED WITH PENICILLIN

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THE SUBJECT of nephropathy in congenital syphilis has received scant attention in the literature. Stokes and associates [1] and Jeans and Cooke [2] commented on the rarity of the condition in their experience. Lereboullet and LeLong [3] in a survey of the literature up to 1930 were able to cite only 15 cases in which renal findings were prominent in syphilitic infants. Herrmann and Marr,[4] reviewing the subject of syphilitic nephropathies, in 1935, indicated that those due to congenital syphilis were latent for the most part and infrequently encountered. Recently, Platou and his associates [5] reviewed 122 cases of congenital syphilis treated with penicillin. No definite cases of nephropathy were seen, with the possible exception of that of 1 infant who showed edema and hematuria early in the course of penicillin therapy. This child recovered uneventfully, and a diagnosis of syphilitic nephritis was not established.

From the Department of Dermatology and Syphilology, Hospital of the University of Pennsylvania, Philadelphia, Donald M. Pillsbury, M.D., director and the Children's Hospital, Philadelphia, Joseph Stokes Jr., M.D., director.

1. Stokes, J. H.; Beerman, H., and Ingraham, N. R., Jr.: Modern Clinical Syphilology: Diagnosis, Treatment, Case Study, ed. 3, Philadelphia, W. B. Saunders Company, 1944, p. 1110.

2. Jeans, P. C., and Cooke, J. V.: Prepubescent Syphilis, in Haynes, R. S.: Clinical Pediatrics, New York, D. Appleton and Company, 1930, vol. 17. p. 316.

3. Lereboullet, P., and LeLong, M.: Heredosyphilitic Nephritis in Nurslings, Nourrisson **18**:367, 1930.

4. Herrmann, L. G., and Marr, W. L.: Clinical Syphilitic Nephropathies: A Study of New Cases and a Survey of Reported Cases, Am. J. Syph. & Neurol. **19**:1, 1935.

5. Platou, R. V.; Hill, A. J., Jr.; Ingraham, N. R.; Goodwin, M. S.; Wilkinson, E. E., and Hansen, A. E.: Effect of Penicillin in the Treatment of Infantile Congenital Syphilis: Further Observations, Am. J. Dis. Child. **72**:635 (Dec.) 1946.

Hutinel,[6] Frank[7] and, more recently, Yampolsky and Mullins[8] touched on the underlying pathologic changes that might be expected in the kidneys of infants with congenital syphilis presenting evidence of renal damage, but as yet there seems to be no general agreement as to the exact histologic picture to be found which might serve as a basis for classification.

With today's more effective and less toxic antisyphilitic therapy, opportunities for future histologic studies of nephropathy associated with congenital syphilis are apt to become increasingly rare. Hence, a clinical rather than a histologic classification assumes practical importance.

Since the manifestations of early congenital syphilis are akin in many respects to those of early acquired syphilis in the adult, it is logical to look to material on the latter subject for a suitable clinical classification. Thomas and Schur[9] accepted the division of syphilitic nephropathies into "syphilitic nephritis" and "syphilitic nephrosis" with the understanding that it is doubtful whether any clearcut line can be drawn between the two in some cases. They pointed out that urinary findings may vary from mild albuminuria with a few unusual elements in the sediment to tremendous albuminuria associated with a few or a large number of casts. Red blood cells may be absent during the entire period of observation, or they may vary in numbers from an occasional cell to almost gross hematuria.

The usual picture of early syphilitic nephrosis as described by these authors is characterized by heavy albuminuria (10 to 30 Gm. in twenty-four hours), casts with but few to no red blood cells and less cylindruria than is observed in true lipoid nephrosis. Renal function is rarely impaired and nonprotein nitrogen remains normal. With blood pressure changes unreliable and inconstantly significant, Thomas and Schur used the degrees of albuminuria and hematuria as the chief criteria in separating nephritis from nephrosis.

It is our belief that the following data should be at hand to establish a clinical diagnosis of congenital syphilitic nephropathy in an infant:

1. Unequivocal concomitant evidences of congenital syphilis and/or consistently positive reaction to serologic tests for syphilis beyond the age of 12 weeks. (Roentgenographically demonstrable infectious osteochondritis and/or periostitis is desirable.)

6. Hutinel, V.: Nephritis in Hereditary Syphilis, Arch. de méd. d. enf. **25**: 577, 1922.

7. Frank, M.: Kidney Affections in Congenital Syphilis, Ztschr. f. Kinderh. **33**:248, 1922.

8. Yampolsky, J., and Mullins, D. F., Jr.: Acute Glomerular Nephritis in an Infant with Congenital Syphilis, Am. J. Dis. Child. **69**:163 (March) 1945.

9. Thomas, E. W., and Schur, M.: Clinical Nephropathies in Early Syphilis, Arch. Int. Med. **78**:679 (Dec.) 1946.

2. Evidence of syphilitic disease in the mother.

3. Unmistakable evidences of nephrosis or nephritis, with causes other than syphilis absent.

4. Prompt disappearance of renal abnormalities on the administration of adequate antisyphilitic therapy and their nonrecurrence.

A case fulfilling these criteria is presented.

REPORT OF CASE

J. G., a 2 month old Negro boy, was admitted July 18, 1946, to the service of Dr. Milton Rappaport, Children's Hospital, Philadelphia. The chief complaint was "swelling of the hands and feet."

The father was under treatment for syphilis at the time the child was admitted. One of three older siblings subsequently proved to have the disease, as did the mother, who had had no serologic studies or treatment for syphilis during pregnancy.

The infant's prenatal and postnatal history was uneventful, and he had appeared to develop normally during the first six weeks of life. Six days prior to admission he became irritable and evidenced pain when handled. Swelling and tenderness of the feet and hands were noted five days later.

Physical examination on admission showed a well developed, well nourished Negro infant who did not appear acutely ill. The weight was 11 pounds 4 ounces (5,103 Gm.). The following abnormal findings were listed: (1) moderate pitting edema of the dorsa of the hands and swelling and tenderness of the proximal portion of certain of the phalanges; (2) moderate swelling and questionable tenderness of the dorsa of the feet; (3) several moist, reddish centimeter-sized plaques of the perianal skin. The liver and spleen were not palpable and the results of the rest of the physical examination were also normal.

Demonstration on roentgenograms of changes in the long bones characteristic of congenital syphilis, as well as the report of a positive reaction to a serologic test for syphilis, confirmed the clinical diagnosis. Other initial laboratory findings, notably a 4 plus reaction for albumin in the urine and a normal level of urea nitrogen in the blood, suggested the diagnosis of nephrosis.

Treatment with aqueous solution of sodium penicillin (90 per cent crystalline G) was instituted on the third day in the hospital. A schedule calling for 6,250 units every three hours for a total of one hundred and twenty-three doses was followed. This corresponded roughly to 70,000 units per pound (150,000 units per kilogram) of body weight over a sixteen day period. Total dosage amounted to 765,000 units.

Six hours after the administration of the initial dose of penicillin, the child's temperature, which had previously ranged from 98.6 F. (rectum) to 99.8 F., rose to 101.3 F. without other apparent clinical change. Within twenty-four hours it had again subsided to its former level. The temperature remained normal, with the exception of a minor rise on the eleventh day of treatment attributable to a reaction to blood transfusion.

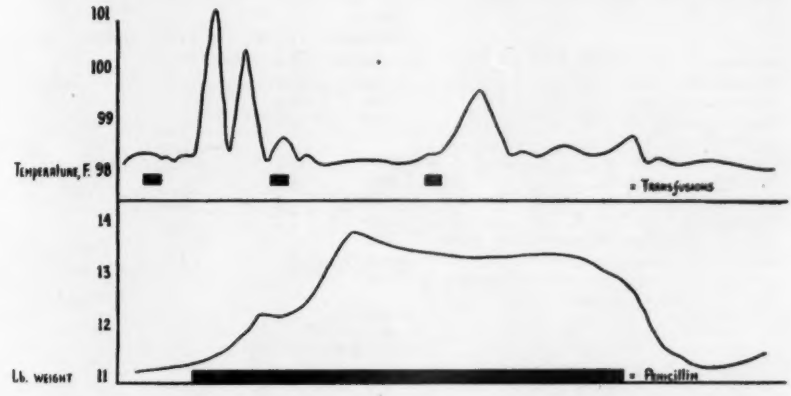
On the third day of treatment, the infant's face became edematous and a decided increase in weight was noted. In the ensuing five days the weight increased still further to 3 pounds (1,361 Gm.) over the level on his admission. Generalized pitting edema was evident.

A consistent 3 to 4 plus reaction for albumin was noted in the urine during the first twelve days of therapy. On the thirteenth day of treatment albuminuria was reported as showing only a 2 plus reaction. By the end of the subsequent forty-eight hours clinical edema was no longer apparent.

Within the first twenty-four hours of therapy the child seemed improved. Bottle nursing was more vigorously pursued, and he was no longer fretful. This clinical improvement was maintained despite the pronounced increase in his edema.

He received during hospitalization three transfusions of from 50 to 75 cc. of whole citrated blood. The third of these was administered on the eleventh day of treatment. Fifteen minutes after completion of the transfusion, dyspnea, wheezing, rales and expiratory difficulties were observed. This reaction was effectively combated by means of oxygen therapy, epinephrine U. S. P. given intramuscularly and diphenhydramine hydrochloride N. N. R. (elixir benadryl hydrochloride®). After several hours no further trouble was encountered.

The urine was free of albumin on the sixteenth and final day of treatment. At the same time, there was a massive diuresis with a drop in weight of more than 1 pound (454 Gm.). At the time of discharge, twenty-six days after his admission, he was still 1 pound over his weight on admission, owing in large part to improved nutrition.



Hospital Days	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
Urine Albumin	4+	4+	4+			4+		3+	3+	3+		3+	3+		3+	1+	tr.		tr.		0		0	0		
" WBC's (HPF)	3	6	7			4		4	3	3		8	8		3	2	2		0		0		Occ.	Occ.		
" RBC's (HPF)	0	2	3			9		8	6	4		18	15		20	5	4		6		5		0	0		
" Casts (gonmam)	0	Occ.	5			2		2	2	Occ.		Occ.	Occ.		Rare	Rare			0		Rare		0	0		

Course in the hospital and treatment given infant with congenital syphilitic nephrosis.

On discharge he was followed in the outpatient department at monthly intervals. Except for minor episodes of infection of the upper respiratory tract, he remained in excellent health. Ten months from the onset of treatment he was readmitted for study. Results of clinical examination at this time were normal, as were findings on laboratory and roentgenologic investigations. He had gained 8 pounds (3,629 Gm.) and was alert and vigorous.

The principal roentgenographic evidences of syphilis on the first admission were increased density of the zones of temporary calcification of the long bones and deep transverse bands of lessened density. There were punched-out areas at the distal ends of the diaphyses indicative of congenital syphilis. Twelve days after institution of treatment with penicillin, there were decided periosteal proliferation and a tendency to metaphysial rarefaction. At the same time deposition of calcium and thickening of the periosteum indicative of healing were noted. Striking regression toward normal was apparent by one and one-half months, with almost complete healing achieved by three and one-half months. The roentgenographic appearance was completely normal ten months later.

COMMENT

Laboratory Studies.—The relative scarcity of red blood cells in the urine in the first five days of hospitalization in contrast to the massive albuminuria strongly favored the diagnosis of nephrosis over nephritis. Supporting evidence was a moderately increased serum cholesterol content and a normal blood urea nitrogen level. A tendency to reversal of the albumin to globulin ratio was noted. Casts were consistently rare in the urine.

Whether the increased numbers of red cells observed in the urine between the third and the twelfth days of treatment were due to the disease process, to a reaction to the penicillin itself or to the citrated whole blood which had been administered could not be determined.

TABLE 1.—*Laboratory Data on Infant with Congenital Syphilitic Nephrosis*

	6/18/46 (Admission)	6/22/46	6/15/46	8/13/46	5/7/47
Red blood cells, millions	3.13	3.9	....	...	...
Hemoglobin, Gm.	9.5	10.0	....	...	...
White blood cells, × 1,000	18.0	20.0	10.0	...	...
Total protein, mg./100 cc.	6.32	....	....	5.6	7.5
Albumin, mg./100 cc.	3.18	....	....	3.5	4.4
Globulin, mg./100 cc.	3.14	....	....	2.1	3.1
Blood urea nitrogen	15.9	....	....	...	13.0
Calcium, mg./100 cc.	8.7	....	....	...	9.4
Phosphorus, mg./100 cc.	4.4	....	....	...	6.0
Alkaline phosphatase, Bodansky units	21.8	....	....	...	10.4
Serum cholesterol, mg./100 cc.	286.0	....	....	...	168.0
Prothrombin time, per cent of normal	100.0	....	....	...	...
Van den Bergh reaction					
Direct	Negative	....	....	...	...
Indirect	Less than 0.5 mg.	....	....	...	...
Vitamin C level, mg./100 cc.	0.28	....	....	...	...
Kadji vitamin C index	15.8	....	....	...	...
Urea clearance	....	....	....	...	94% of normal
Phenolsulfonphthalein test	Dye appeared in 4 min.; 23% excretion in first 15 min.				

The albumin to globulin ratio was found to be within normal limits by the twenty-sixth day in the hospital, and it was normal ten months later. There were no urinary abnormalities twenty-four hours after completion of penicillin therapy, and results of studies of renal function again in the tenth month of follow-up observation were entirely normal.

Dosage.—Selection of full initial doses of penicillin as were used in this patient is in keeping with the practice of such authors as Platou and his associates,[5] Rose, György and Ingraham,[10] and Heyman and Yampolsky.[11] Rose and her co-workers stated that

> . . . the so-called Herxheimer reaction is not to be feared and . . . in the debilitated infants . . . it is even more desirable to give larger initial dosages to offset possible secondary infection.

10. Rose, E. K.; György, P., and Ingraham, N. R., Jr.: Penicillin in the Treatment of the Syphilitic Infant, J. Pediat. **29**:567, 1946.

11. Heyman, A., and Yampolsky, J.: Treatment of Infantile Congenital Syphilis with Penicillin, Am. J. Dis. Child. **71**:506 (May) 1946.

Our patient's definite febrile reaction at the outset of treatment, with a subsequent exacerbation of his edema, was strongly suggestive of a Herxheimer reaction. Even had such a response been anticipated, we would not, in the light of the experience of these other authors, have felt justified in modifying the prearranged schedule of therapy. Scott and Clark [12] reported a renal Herxheimer reaction following penicillin therapy in a patient with secondary syphilis in whom the favorable outcome did not at any time seem in doubt. It is likely that the patient previously mentioned in the series reported on by Platou and associates also had a renal Herxheimer reaction. Here again, the final result was perfectly satisfactory.

Clinical Course.—Olansky [13] reported excellent results in the treatment of a patient with nephrosis associated with seropositive primary syphilis on whom he employed oxophenarsine hydrochloride U. S. P. (mapharsen®) by intravenous drip and in another patient with secondary syphilis for whom he used penicillin in oil and white wax

TABLE 2.—*Serologic and Spinal Fluid Response*

	Blood		Number of Cells	Cerebrospinal Fluid		
Date, 1946	Kolmer Reaction	Kline Reaction		Colloidal Mastic Reaction	Wassermann Reaction	Protein, Mg./100 Cc.
7/10	44—	256 units	0	Negative	Negative	20
7/30	44—	256 units	..	.....	.....	..
9/13	44—	128 units	..	.....	.....	..
10/22	44—	32 units	..	.....	.....	..
11/15	00—	Negative	..	.....	.....	..
1947						
2/18	00—	Negative	..	.....	.....	..
4/ 4	00—	Negative	..	.....	.....	..
5/ 7	00—	Negative	0	Negative	Negative	10
6/ 9	00—	Negative	..	.....	.....	..

U. S. P. Thomas and Schur [9] obtained equally satisfactory results with penicillin in 3 patients with nephrosis associated with secondary syphilis. The clinical course of our patient was comparable.

Serologic Response.—Rose and her co-workers [10] showed that the average time for serologic reversal in 36 infants with active congenital syphilis was one hundred and fifty-four days following dosages of penicillin of 20,000 units per pound or more. Our patient's reaction became seronegative by the fourth post-treatment month.

Prognosis.—Thomas and Schur [9] stated the opinion that early (acquired) syphilitic nephropathies leave no demonstrable sequelae after adequate therapy. At the end of ten months none was demonstrable in our patient and his then normal growth and development gave every indication of continued excellent health.

12. Scott, V., and Clark, E. G.: Syphilitic Nephrosis as a Manifestation of a Renal Herxheimer Reaction Following Penicillin Therapy for Early Syphilis: Case Report, Am. J. Syph., Gonor. & Ven. Dis. **30**:463, 1946.

13. Olansky, S.: Syphilitic Nephrosis: A Report of Two Cases, J. Ven. Dis. Inform. **28**:45, 1947.

SUMMARY

A report of an infant with congenital syphilitic nephrosis who was successfully treated with penicillin is presented. Full dosages of penicillin were used throughout therapy without untoward reaction. Prompt remission of the abnormal urinary findings coincided with the completion of the treatment schedule of 150,000 units of penicillin per kilogram of body weight, given every three hours over a sixteen day period.

Roentgenographic findings were near normal by one and one-half months after institution of treatment, with almost complete healing by three and one-half months. Reversal of the serologic reaction occurred by the end of the fourth month. Physical findings, results of laboratory studies and roentgenographic appearance remained normal through eleven post-treatment months.

150 North Eleventh Street.

DIABETES MELLITUS ASSOCIATED WITH MONGOLISM

A Case of a Child Two Years of Age

HARRY G. JACOBI, M.D.
AND
JULIAN L. ROGATZ, M.D.
NEW YORK

THE COMBINATION of mongolism and diabetes poses an interesting and unusual problem. According to the available reported observations with respect to carbohydrate metabolism in mongolism,[1] there occurs a definitely delayed glycemic response in this condition. Such a delayed glycemic response has been repeatedly demonstrated by means of dextrose tolerance tests. These were invariably characterized by low, absent or delayed peaks in the concentration of the blood sugar following the ingestion of the dextrose. With advancing age, these mongolian idiots showed this tendency in increasingly more pronounced form. The onset of diabetes at the age of 2 years being in itself quite uncommon, the combination of this condition with mongolism is a most unusual occurrence and probably acounts for the rarity of reports of such cases in the literature.

Lawrence,[2] who reported on the only 3 patients we could find on record, was of the opinion that his were the first mentioned in the literature. Each of his patients gave a positive hereditary history of diabetes. His first patient, a girl, 10 years of age, showed 4 to 6 per cent sugar in the urine and was adjusted at a level of 20 units of insulin given twice daily. The second patient, also a girl, aged 12 years, had diabetes since 5 years of age and was controlled on insulin, 6 to 16 units administered twice daily. The third child was a boy, whose diabetes had appeared at the age of 10 years, with 5 per cent sugar in the urine. His diabetes was controlled with insulin, 14 units given in the morning and 8 units at night.

In attempts to account for the observed carbohydrate response in mongolism, various explanations have been offered. The exact interpretation of these observations, however, definitely projects the subject into the realm of theoretic possibilities. One can conclude definitely

From the Department of Medicine, Lenox Hill Hospital (Dr. Jacobi, attending physician) and the Abraham Jacobi Division for Children, Lenox Hill Hospital (Dr. Rogatz, attending pediatrician).

1. (*a*) Bixby, E. M.: Biochemical Studies in Mongolism, Proc. Am. A. Ment. Deficiency **63**:59, 1939. (*b*) Bixby, E. M.: Further Biochemical Studies in Mongolism, Am. J. Ment. Deficiency **45**:201, 1940. (*c*) Benda, C. E., and Bixby, E. M.: Function of the Thyroid and the Pituitary in Mongolism, with Report on Blood Groups of American Mongoloid Defectives and Comments on Determination of Cholesterol, Am. J. Dis. Child. **58**:1240 (Dec.) 1939. (*d*) Bixby, E. M.: Glucose Tolerance and Insulin Tolerance in Mongolism, Am. J. Ment. Deficiency **47**:158, 1942.

2. Lawrence, R. D.: Three Diabetic Mongol Idiots, Brit. M. J. **1**:695, 1942.

from all these studies that there does exist in persons with mongolism a distinctly abnormal metabolism of sugar quite similar to that observed in patients with pituitary dysfunction and that the occurrence of the delayed glycemic response in these states is not the result of either a lack of insulin or an increased resistance to it. If anything, mongolian idiots have been observed to show slight increase in their sensitivity to insulin.[1c, d]

We, therefore, wish to present this additional case report, since it represents the youngest patient to have this unusual combination of mongolism and diabetes.

REPORT OF A CASE

Our patient was a male infant, 2 years of age, who was observed by one of us since birth. His most recent complaint was excessive thirst and increased frequency of urination of one week's duration. The child was seen by a local physician, who found sugar in the urine. This was confirmed when the examination of a specimen was repeated at the office of one of us and it was found to contain reducing substances. The patient was then admitted to the Lenox Hill Hospital for further study.

Present Illness.—The infant had been well until two months before admission when a series of "colds" of short duration occurred. They culminated in a more stubborn infection of the nose and throat, characterized by a running nose and a nonproductive cough. The appetite was poor during this period.

One week prior to his admission the mother noticed that the child became thirsty and drank excessively, requiring as much as six glasses of water daily. He had decided increase in urinary frequency both day and night.

Previous History.—The patient was the third child, born by cesarean section and weighing 6 pounds 8 ounces (2,948 Gm.) at birth. The first sibling died thirteen years ago when 8 days old, cause of death unknown; the second was 11 years old and well. At the time of the patient's birth the mother was 40 years old and the father was 45. There was a definite history of diabetes in the family, the paternal grandfather and one paternal aunt and uncle having the disease.

The patient's appearance at birth strongly suggested mongolism. This diagnosis was repeatedly confirmed by many examiners. The first teeth appeared at 8 months. The child walked at 20 months.

Physical Examination.—Examination showed a moderately alert, white male infant, not acutely ill, with the characteristic appearance of mongolism, the more prominent stigmas being the facies, with upward and outward slanting of the palpebral fissures, slight bilateral epicanthus, redundant skin of the neck, generalized hypotonicity and hyperextensibility of the joints. The infant did not talk, but the parents were impressed by his response to musical rhythms. He had thirteen teeth. The tonsils and adenoids were hypertrophied and cryptic. A loud, over-all, systolic murmur was repeatedly heard over the entire precordium. The edge of the liver was palpable about 3 cm. below the infracostal margin. His height was 33 inches (84 cm.), and his weight was 22 pounds (10 Kg.).

The patient received a sugar tolerance test at the time of his admission to the hospital for which 24 Gm. of glucose was used. The blood sugar values in venous blood were 166 mg. on fasting and 300 mg. at forty-five minutes. At two hours after ingestion of glucose the blood sugar level was 310 mg. per hundred cubic centimeters.

He was placed on a diet of protein, 35 Gm.; fat, 35 Gm., and carbohydrate, 125 Gm. Regular insulin was given as indicated by the results of urinary examinations

done before meals and also at 9:30 p. m. The amount of regular insulin administered was according to the following schedule: 1 plus reaction for sugar, no insulin; 2 plus reaction, 5 units of insulin; 3 plus, reaction, 5 units, and 4 plus reaction, 10 units. After several days of observation, it was concluded that the infant required an average of 10 units of regular insulin daily. Twenty-four hour samples of urine were also collected to determine the amount of glucose excreted for each such period. Further observation necessitated a slight change in his diet to protein, 45 Gm.; fat, 35 Gm., and carbohydrate, 110 Gm. The insulin had to be increased to 8 units in the morning and 5 units at night—a total of 13 units a day. The urinary excretion of sugar varied from 1 to 5 Gm. in the twenty-four hours.

Under this regimen the patient's weight increased during his stay of ten days at the hospital from 22 to 25 pounds (10 to 11.3 Kg.), and his general condition showed a definite improvement. A fasting blood sugar test, repeated after four days of this regimen, revealed 133 mg., with the carbon dioxide-combining power of the blood plasma at 41.4 volumes per cent. Just prior to his discharge from the hospital the fasting blood sugar level was 100 mg. per hundred cubic centimeters, and the urine was free from sugar. The child is being followed at his home, and the diabetes has remained under good control on the aforementioned regimen.

COMMENT

One is always attempting to offer explanations for observations which show deviations from the normal trend. The correlation of cause and effect, however, can occasionally lead into the field of speculation, which we definitely wish to avoid. Our patient, who had been under careful pediatric observation since birth, showed the definite symptoms and signs of mongolism. Studies on the carbohydrate metabolism of such persons have revealed a notably delayed glycemic response, indicating a pronounced increase in tolerance for carbohydrates.

What, then, are some of the factors that may be considered significant in the reversal of this increased carbohydrate tolerance, even to the point of producing diabetes? The most important factor is undoubtedly that of heredity. In our patient the evidence was quite definite. The paternal grandfather showed evidence of diabetes at the age of 76 years. One paternal uncle had the disease at 39 years of age and one paternal aunt at 35 years.

The second significant factor is that of infection. Our patient had been having repeated infections of the upper respiratory tract for about four weeks prior to the onset of diabetic symptoms. Thus, a primary, factor of heredity was present, with a contributing, secondary factor in the form of infection. Both of these were potent enough to overcome the natural, nondiabetic tendency usually observed in persons with mongolism, a tendency which also accounts for the infrequency of such case reports in the literature. There is no evidence thus far to suggest an etiologic relationship between diabetes and mongolism.

SUMMARY

A case of diabetes mellitus in a mongolian idiot, 2 years of age, is described. A brief review of the existent literature, which offers no similar report on a patient so young, is given, and a short discussion is included.

111 East Seventy-Sixth Street.

Progress in Pediatrics

PEDIATRIC REPORT ON MEDICAL CONDITIONS IN THE VIRGIN ISLANDS

HEYWORTH N. SANFORD, M.D.
CHICAGO

THE GENERAL health of the children in the Virgin Islands is not good. While the condition in the urban areas is fair, those in the rural areas suffer from gross malnutrition. This is not due to any lack of particular foods or vitamins but to a general lack of food. One never sees a fat child. They are all thin and undernourished. This is particularly pitiful, for these children are not neglected, but are clean and well cared for. I did not see a dirty or neglected child on the islands.

From a public health standpoint their care is adequate. A good effort is made to immunize the children for diphtheria, tetanus and whooping cough by three injections given in the period of from 1 to 5 years of age. The small size of the area of the individual islands gives the public health nurses an opportunity to contact almost all the children, provided they are given satisfactory transportation. Even with their limited facilities, coverage is almost complete. Needless to say, none of these diseases for which immunization is available was seen. The children are also vaccinated for smallpox during this age period.

Well baby clinics are conducted once or twice a week in the principal cities and also at schools in the rural areas. Theoretically, none of the mothers should have to bring the children more than 2 miles (3.2 kilometers) for these. Practically, 2 miles' walking over rough roads carrying a baby makes this more of a task than it would appear. However, the attempt is made and good work is done at these clinics. School examinations are also made by the local health commissioner and his assistant as far as possible.

CARE ON ST. THOMAS AND ST. CROIX ISLANDS

Sick children on St. Thomas Island are cared for at the Municipal Hospital at Charlotte Amalie. There are twenty pediatric beds, under the supervision of a pediatrician trained in the continental United States. Their occupancy was mostly taken up with children with

Report of the pediatric member of the American Medical Association Commission of the United States Department of the Interior.

malnutrition and various infections who were sent in from the rest of the island. Their care was adequate and the nursing supervision satisfactory. The nursery for the newborn is equipped for 14 infants and is under pediatric supervision. There is also a small premature unit separate from the nursery. The hospital is well run and the care of the children in general is satisfactory.

On St. Croix Island the picture is somewhat different. Here sick children are cared for in the general hospitals of Fredericksted and Christiansted. Fredericksted, a town of 2,500, has a sixty bed municipal hospital, with twelve beds devoted to children. At the time visited, their occupancy was with children with malnutrition, heart disease and respiratory disturbances. The ward was kept very clean but was cramped for space. The building is 150 years old and has been rebuilt many times. It is entirely inadequate. There are only two doctors for the entire hospital. They are first class men, trained in the continental United States. There are only three nurses and a few nurses' aides. Maternity patients are kept seven to ten days, if there is no shortage of beds. The hospital had a small nursery for newborn infants and one incubator for premature infants. There is no nursery supervision and, owing to the shortage of nurses, the babies are kept with the mothers as much as possible. Thus, because of inadequate nursing, they are unconsciously adopting a modern procedure.

In Christiansted, a town of about 5,000, there is a municipal hospital with the same number of beds. This is more modern, but it is somewhat inaccessible for sick persons, being built on a hill above the town. Some rebuilding is going on and there will be a ward for fourteen pediatric beds when it is completed. The same physicians alternate here with the Fredericksted hospital, and the general care and occupancy is much the same. The nursing care for the pediatric ward is entirely inadequate; one nurse is on duty all day and there is none on duty at night.

COMPENSATION RATES

In the medical service for the islands there are two separate rates of compensation for the same service. Nurses under municipal pay receive considerably less ($60 to $75 per month) than those under the public health service ($100 to $125 per month). This is also true of the hospital personnel. For example, a chief laboratory technician receives $110 and his assistant $60 per month. Both are on municipal pay. A junior, doing the same work as the assistant, receives $110 per month from the veterans' service. This obviously does not lead to the best of feeling; but I must admit that this information was obtained with difficulty, and the workers are not complaining

in any sense of the word. This was the surprising observation about the attitude of all medical workers. They were thankful for what they had and were trying to do the best they could under poor surroundings.

CONCLUSION

The entire medical situation from a pediatric standpoint is bad. The system should be revamped to place all workers under one head and on a fair basic scale of pay. The salaries for all are too low. The hospitals are old and in bad condition. These should be replaced, with double the bed capacity. More money should be alloted for equipment. Any group of persons who can work under such handicaps as carrying every bit of water to all floors of the hospitals and heating water to sterilize instruments with a charcoal burner deserve some help. If they can accomplish so much under such handicaps, certainly they could do much more if given adequate assistance. Lastly, some adjustment must be made to increase the incomes of these poor people. They are our own citizens and are entitled to our help.

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PEDIATRIC REPORT ON MEDICAL CONDITIONS IN PUERTO RICO

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CHICAGO

THE GENERAL health of the infants and children of Puerto Rico is as good as might be expected in a tropical climate and under the existing conditions of nutrition of the entire population. The infants are spared the usual digestive disturbances and infections of the first year of life by the fact that most of them are breast fed for the greater part of that year. If any supplementary feedings are given, they are usually beans and rice, the staple diet of all the islanders. There is, no doubt, a lack of vitamin A in their diet if the breast milk is deficient, as fresh cow's milk, butter and eggs are rarely used. This may account for the unexpected number of respiratory disturbances seen in these children. Colds, bronchitis, pneumonia and laryngotracheobronchitis are common. If milk is given, the dried milk products are mostly used, although evaporated milk is now becoming popular.

HEALTH OF CHILDREN

After the first year of life, when the child is weaned, the picture changes. Now the principal article of diet is carbohydrate, rice and beans. The beans used are usually of a low protein content. Protein is, therefore, lacking in the diet because the family, if they own a cow or chickens, will sell the milk and eggs rather than keep them for the family's own use. This results in gross malnutrition, represented by hypoproteinemia. Its signs are generally edema, more prominent in the abdomen and face, with loss of weight and anemia. Children with this condition are seen in all the pediatric wards of the general hospitals. They respond to added protein in the diet, provided they do not fall prey to an intercurrent infection. These children lack vitamin A and, frequently, vitamin C. The islanders do not like or, through a mistaken idea of the cause of gastrointestinal disturbances, are loathe to use their own home-grown fruits but rely on canned fruit juices that have little vitamin value. Some active scurvy is seen, and infections, such as osteomyelitis, are frequent. Another common condition is a glomerulonephritis following cutaneous infections such as impetigo. The outdoor life of the majority of the children makes rickets mild, if present at all.

Report of the pediatric member of the American Medical Association Commission of the United States Department of the Interior.

Surprisingly few gastrointestinal disturbances occur in the children. Bacillary forms of dysentery are not common in the younger children, and typhoid fever has been practically eliminated by public health measures. It is estimated that the incidence of Amoeba infestations is only 3 per cent, Giardia 20 per cent and Trichuris 90 per cent. This means that about 1 in 5 of the children harbor Giardia, and nearly all have Trichuris. However, there is no clear evidence that Giardia is pathogenic for them, and, while trichuriasis may cause some mechanical difficulties, and no doubt contributes to the anemia present in almost all the children, it is not otherwise specifically harmful to them.

Almost all the children are anemic by our standards. Those admitted to the hospital show a hemoglobin content of 6 to 10 Gm. of hemoglobin per hundred cubic centimeters of blood, with corresponding depletion of red cells; frequently, less than 6 Gm. is found when an infection is present. This is also a contributing factor to infections such as osteomyelitis and nephritis and makes the care of any ill child a double therapeutic problem.

CONTAGIOUS DISEASES

From a public health standpoint, measles and whooping cough exist as in the continental United States. Scarlet fever as seen in continental United States is rare and rabies is unknown. Diphtheria is seen occasionally. The Public Health Service immunizes all children for diphtheria who are brought to the various hospitals and dispensaries, but due to the nursing shortage there has been no concerted follow-up program to immunize all infants. Tetanus is not uncommon and represents from 1 to 5 per cent of all pediatric admissions in some localities. This condition is oftenest caused by infected chigger bites, while tetanus neonatorum is occasionally seen. A combination of immunizations against tetanus and diphtheria would eliminate many of these cases, and it is understood that the health commissioner, who is aware of this condition, is about to put such a procedure into effect. Vaccination against smallpox is done on all infants brought to dispensaries and hospitals, and there is no smallpox. Immunization for typhoid is also done, but typhoid is not a problem.

WELL BABY CLINICS AND PEDIATRIC SERVICES

Well baby clinics are held with regularity in the district and municipal hospitals in the metropolitan areas. In these districts the public health nurses are active in encouraging mothers to bring their children to clinics. There is a lack of such in the rural areas. In the district hospitals the well baby clinics are held in conjunction with the outpatient clinics and are well conducted. In Rio Piedras district and

municipal medical care is combined in one health center. This has resulted in an excellent well baby service that will, no doubt, be duplicated throughout the island.

Pediatric services in the island are divided between the municipal and the district hospitals under the Insular Public Health service, headed by the health commissioner. The municipal hospitals are inadequate. The care given depends on the political management of the units and on the physician in charge. The municipal physician, if pediatric minded, will do excellent work, as has been noted in some of the smaller communities. In one community observed (San German), the municipality paid a hospital operated by a Catholic sisterhood to care for the indigent children of the city. These children were well cared for. The City Hospital of San Juan has a well conducted pediatric department. Thus, good pediatric care can be given under proper management.

The Public Health Service under the commissioner of health operates hospitals in four districts, corresponding to our counties, in the northern part of the island: Fajardo, Arecibo, Bayamon and Aguadilla. These hospitals have adequate pediatric beds and a gross admission of 1,000 pediatric cases each a year. The wards are well organized and clean and have a cheerful atmosphere. The nursing service is inadequate, as with us, but, considering the lack of personnel, well done. The food is clean, well balanced and well served. The pediatric service consists of an intern (or assistant resident), resident and attending pediatrician. These are all full time men, each of whom has been educated, as a rule, in a medical school in the continental United States. The chief, or attending pediatrician, has had postgraduate pediatric training. Outpatient and well baby clinics are operated in conjunction with the pediatric departments and are well managed.

Each of these hospitals has a contagious unit of twelve beds under the control of the pediatric department. The pediatric surgical cases and the nursery for the newborn are also under this department. In the maternity departments the mothers are kept from three to five days after delivery. Breast feeding is advocated and few instances of any formula feedings were seen. The dry technic of skin care is used. The nurseries are well managed, and the technic is good. Premature infants are kept in the nurseries for the newborn. Incubators and premature feeding technic are used as far as nursing personnel will permit. Epidemic diarrhea of the newborn has never been seen on the island, and cutaneous infections are infrequent among the newborn.

The pediatric care of the sick children is excellent, and the pediatricians are well acquainted with all the accepted methods of treatment. As many transfusions as possible are given, but they are handicapped by the lack of a blood bank, except in Bayamon where blood can be obtained from the bank at the School of Tropical Medicine in San Juan. They

problem is that of a satisfactory donor. The child's relatives or parents are, as one pediatrician expressed it, "so much in need of a transfusion themselves" that it is hard to find a healthy donor. While the budget must be squeezed, most of the hospital administrators are able to furnish adequate supplies of penicillin, streptomycin and other necessary pharmaceutic preparations.

The San Juan City Hospital is the one municipal institution that is the equal of the district hospitals. Here, as stated previously, the pediatric care is excellent and all manner of necessary laboratory examinations are made. Every effort is also put forth to make this a teaching hospital, as well as a clinical one. Since San Juan is the largest city, it is easier to keep a staff here than in some of the more isolated communities. Probably a salary increase or arrangements for time off for study will have to be made in the more outlying district hospitals to encourage the competition between the higher compensation of private practice and the salaries paid in the veterans' hospitals.

In San Juan, the City Hospital handles the majority of the pediatric cases rather than the one church hospital and the many small private clinics. However, in Ponce, the second largest city, the majority of pediatric practice is done in the Pila clinic, a private institution. This has a three hundred bed hospital and clinic where 300 maternity patients are delivered a year. There are about fifteen pediatric beds. It has an excellent nursery for newborn infants. The pediatric department and the nursery for the newborn are under the care of a well qualified pediatrician and are the equal of any seen in pediatric service.

CARE OF SCHOOL CHILDREN

In San Juan, the School Hygiene Clinic for school children is excellent. Here all school children are given a yearly examination for general health and microroentgenograms of the chest are taken. At the time of our visit, a survey of 800 children of school age had just been completed and 4 children were found to have tuberculosis; this is an incidence of 0.5 per cent and is representative of the surprisingly small incidence of tuberculosis in the island children.

CONCLUSION

On the whole, it may be stated that the pediatric care of the children in the large cities under the supervision of the Insular Public Health Service and the health commissioner is adequate. Salary adjustments to hold existing personnel will, no doubt, be made, as the commissioner is well aware of such discrepancies. The weak link is the municipal hospitals. These should be taken out of political control. As a substitute, the district hospital program might be extended. At the present,

the health commissioner is working out a scheme of combining the public health station with a municipal hospital in a community under one head and has begun some of these buildings. They have not been completed but may solve the problem. It will also be necessary to extend the follow-up studies of clinic patients, well baby immunization and care by the public health nurses as rapidly as these can be secured. In the metropolitan areas the pediatric beds are adequate for present occupancy and either of the aforementioned plans should improve the pediatric care in the rural districts. Besides this, the problem of inadequate diet with accompanying malnutrition is basic for all the island and must be solved if health is to be maintained.

952 North Michigan Avenue.

Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

ON THE SUSCEPTIBILITY OF MACACUS RHESUS TO THE VIRUS OF TICK-BORNE ENCEPHALITIS. L. A. SILBER and A. K. SHUBLADZE, Am. Rev. Soviet Med. **2**:332 (April) 1945.

Silber and Shubladze studied the susceptibility of monkeys to tick-borne encephalitis. Monkeys were inoculated with brain emulsions from recent fatal human cases of the disease and with brain emulsions of mice infected with subcultured strains of tick-borne encephalitis. All the subcultured strains killed the mice after intracerebral injection in a dilution of 1 : 1,000,000 and were equally neutralized with the serums of convalescent patients and with the serums of immunized rabbits. Ten per cent brain emulsions were prepared either with Tyrode's or with Ringer's solution. The monkeys were inoculated intracerebrally, intravenously and intranasally and were under observation for three months unless they died earlier. The brain, blood, liver and spleen of the animals were examined for virus content by intracerebral inoculation of mice. The brain and other organs of the monkeys were subjected to histologic examination by A. G. Kestner. The serums of the surviving monkeys were tested for virus-neutralizing antibodies.

The authors conclude that Macacus rhesus monkeys are susceptible to the virus of tick-borne encephalitis but that the disease is not always fatal. Of 9 monkeys given inoculations in the cerebrum and spinal cord, 3 survived. Intravenous inoculation of 2 monkeys and nasal inoculation of 1 monkey proved ineffective.

The incubation period in Macacus rhesus lasts five to nine days, and the average duration of the disease is six to eleven days. The chief symptoms are fever and paralysis of the forelimbs and hindlimbs.

The disease is an acute meningomyeloencephalitis.

Serum antibodies which neutralize the virus of tick-borne encephalitis appear in convalescent monkeys. The antibodies occur late in the disease and are apparently retained in the serum for a long time after recovery. Residual paralysis of the upper extremities is seen in convalescent monkeys and resembles that seen clinically.

The virus of tick-borne encephalitis differs from that of the Japanese summer and the St. Louis type. Louping-ill occupies an intermediate position between St. Louis and the Japanese encephalitis.

GUTTMAN, Philadelphia [ARCH. NEUROL. & PSYCHIAT.].

STUDIES ON INFECTION WITH BACILLUS ANTHRACIS: VII. A COMPARISON OF THE ANTIBACTERIAL EFFECTS OF CALF THYMUS HISTONE AND A QUATERNARY AMMONIUM CATIONIC DETERGENT ON B. ANTHRACIS. NORMAN WEISSMANN and LLOYD H. GRAF, J. Infect. Dis. **80**:145 (March-April) 1947.

Experiments carried out in a Warburg apparatus showed that the quaternary ammonium detergent Zephiran® (benzyl-dimethyl-alkyl ammonium chloride) was able to inhibit completely the oxygen uptake of suspensions of Bacillus anthracis. Lecithin was capable of completely neutralizing the antibacterial action of the detergent.

Calf thymus histone was shown to stop oxygen uptake in suspensions of B. anthracis. Thymus desoxyribonucleic acid neutralized the antibacterial action

of histone. Lecithin caused a delay in histone action, but could not halt it completely. Desoxyribonucleic acid had no effect on detergent activity.

The mechanism of histone action is discussed, and a working hypothesis presented. The probable importance of the lysine content of the natural antimicrobial factors is discussed.

TOOMEY, Cleveland.

Metabolism; Infant Feeding; Milk and Other Foods

ACIDOSIS AND BICARBONATE SEROTHERAPY. L. RIBADEAU DUMAS and MAX LÉVY, Arch. franç. de pédiat. **3**:124, 1946.

In a clinical and therapeutic study of acute dyspepsias in nurslings made by Rohmer (*Arch. franç. de pédiat.* **2**:133, 1944-1945) the intimate relation between albuminuria, especially cylindruria, and disturbances of digestion was emphasized. The author expressed the opinion that in few cases of acidosis was a toxic syndrome revealed. Rohmer announced that while acidosis has for many years been considered as one of the manifestations of the choleriform state, in reality it already exists in all grave dyspepsias of the young infant. It may be provoked by the loss of fixed bases, by the retention of sodium in cells becoming more hydrophilous and possibly also by the increase in blood chlorides. In acute dyspepsias, however, the origin of acidosis apparently lies in the exaggerated production of organic acids following gross disturbances of metabolism. Inorganic acidity appears to be rare and secondary.

Hastings and others expressed the belief that the living cells are not permeable by the chloride ion, the red cells being the only exception. The permeability of the tissues for chloride depends, according to Vlès, on the existing isoelectric index, which varies much from one tissue to another, and the elevation of the erythroplasmatic relation does not necessarily signify that there may exist in a given case a chloropexia parallel in the tissues.

These conclusions of Rohmer are challenged in the present monograph. They are not in accord with the studies of Dumas and Lévy, who base their contention on a series of 580 examinations begun in 1937. It is declared that this disagreement is founded on two fundamental principles which are discussed in detail and concern the role of chloride in the metabolism of water and the renal function.

The authors aver that competent clinicians no longer use injections of saline solutions in the management of toxic states with dehydration on the ground that the toxemia may actually be aggravated (Marfan) and diuresis delayed.

Serotherapy should be adapted to the case in question and bicarbonate, dextrose or chloride solutions used with full knowledge of the indications in each category. Czerny and his associates, as far back as 1897, recommended the use of bicarbonate orally in treatment of the acidotic syndrome. This view was advanced also by Howland and Marriott. The authors began the employment of bicarbonate intraperitoneally in 1922, especially in cases of diabetes mellitus. Finally, Dumas and Lévy adopted the method of using bicarbonate in isotonic solution and in large amounts under the immediate control of a responsible laboratory. The method is now in general use in Denmark, where Esben Kirk has made significant contributions.

AMESSE, Denver.

USE OF CARROT SOUP IN INFANTILE DYSPEPSIAS. C.-A. APFFEL, Arch. franç. de pédiat. **3**:142, 1946.

A new era in the therapeutics of infantile diarrhea was ushered in with the use of vegetable pectins. Moro (1939) introduced carrot soup as a satisfactory and inexpensive medium for pectins in the management of digestive disorders, and the author has carried on investigations during the past four years to confirm, if

possible, Moro's results. In the present article, he expresses considerable enthusiasm for this addition to the pediatrician's armamentarium and discusses its mode of action. The soup can be offered during the earliest days of life and even to premature infants; it may be used to dilute the milk ration or as an excipient for powdered milk.

AMESSE, Denver.

RESTORATION OF WATER IN THE ORGANISM. P. FERENCZ and R. PÁLFY, Orvosok lapja **2**:92 (Jan.) 1946.

Supplying the necessary fluid in cases of great loss of water in infancy often causes difficulty. According to Ferencz and Pálfy, the most favorable location for injection of fluids is the inner surface of the thigh. They have given isotonic sodium chloride solution by the drop method. This method allows 500 Gm. of fluid to be given subcutaneously in four to five hours. The child must be restrained, but usually this does no harm, and there are no pathologic changes in the skin.

GÖGÉNYI-GÖTTCHE, Budapest, Hungary.

QUANTITATIVE BREAST-MILK SECRETION. HANS LADEGAARD PEDERSEN, Ugesk. f. læger **107**:997 (Nov. 22) 1945.

A study was made of the milk secretion in 250 mothers of newborn infants. Giving the infant both breasts at each meal during the whole first week of life caused more rapid development of the milk secretion, and the infants gained weight faster. This effect is without relation to the weight at birth. There was no evident effect on the frequency of hypogalactia. Individual action is recommended in breast feeding in regard to the numbers of nursings and the choice of one or both breasts at each meal.

WALLGREN, Stockholm, Sweden.

Vitamins; Avitaminoses

INTOXICATION RESULTING FROM THE ADMINISTRATION OF MASSIVE DOSES OF VITAMIN D, WITH REPORT OF FIVE CASES. G. W. COVEY and H. H. WHITLOCK, Ann. Int. Med. **25**:508 (Sept.) 1946.

A report based on a study of 5 adults indicates that vitamin D in doses exceeding 150,000 U. S. P. units daily is a toxic substance which produces parenchymatous injury, especially in the kidney.

READING, Galveston, Texas.

STUDIES OF THIAMINE METABOLISM IN MAN: I. THIAMINE BALANCE. THE NORMAL REQUIREMENT OF VITAMIN B_1 AND THE ROLE OF FECAL THIAMINE IN HUMAN NUTRITION. BENJAMIN ALEXANDER and GRETA LANDWEHR, J. Clin. Investigation **25**: 287 (May) 1946.

A man aged 35, weighing 180 pounds (81.6 Kg.) and eating a well balanced diet of approximately 2,400 calories, was studied. Balance studies on thiamine were performed while the subject was allowed dietary freedom and while he received in addition to the diet 0.5 to 145 mg. of thiamine hydrochloride U. S. P. daily by intramuscular injection.

The "minimal requirement" was defined as "that amount of any material which is utilized or otherwise altered in body metabolism plus what is needed to cover all uncontrollable losses from the body." Accordingly, the difference between ingested thiamine and urinary thiamine was considered equal to the minimal requirement.

The minimal requirement in a normal man whose daily intake was 2,400 calories was observed to be 0.44 mg. per thousand calories.

The concentrations of thiamine and cocarboxylase in the feces were remarkably constant and were in the same relation as in the tissues. Most of the fecal thiamine resulted from intestinal biosynthesis and existed in the bodies of fecal organisms. Absorption from the large bowel did not occur when thiamine hydrochloride and cocarboxylase were administered in physiologic amounts by retention enema.

FROM THE AUTHORS' SUMMARY.

KIDNEY FUNCTION AND CIRCULATORY COLLAPSE: POST-SYNCOPAL OLIGURIA. C. BRUN, E. O. E. KNUDSEN and F. RAASCHOU, J. Clin. Investigation **25**:568 (July) 1946.

Syncope was produced in 16 water-loaded human subjects by maintenance of passive erect posture on a tilt table. During the postsyncopal period, after the brief fall in blood pressure, the urine flow was diminished, a urine of higher specific gravity was produced and the urine-plasma inulin (inulin U/P) ratio was increased. Both glomerular filtration rate (inulin clearance) and effective renal plasma flow ("diodrast" [iodopyracet] clearance) were reduced. Glomerular filtration was restored to normal in the latter part of the period of oliguria.

The oliguria, high specific gravity of urine and high urine-plasma inulin ratio, with normal glomerular filtration rate, were attributed to increased reabsorption of water by the renal tubules in response to increased secretion of the antidiuretic hormone of the posterior lobe of the pituitary. Experimental support for this hypothesis was threefold: 1. Blood from 3 erect subjects during syncope in the erect position was transfused into other subjects who were horizontal, and immediately severe, sustained oliguria was induced in the recipients. Blood from the controls in horizontal position had no such effect. 2. Urinary concentration of chlorides during postsyncopal oliguria was elevated, although the total chloride output was normal or low. 3. Postsyncopal oliguria in 2 patients with moderate diabetes insipidus was of shorter duration than in normal persons.

BRODSKY, Cincinnati.

ICE CREAM AS A SOURCE OF RIBOFLAVIN, CAROTENE AND ASCORBIC ACID. A. D. HOLMES, J. W. KUZMESKI, CARLETON P. JONES and F. T. CANAVAN, New England J. Med. **234**:47 (Jan. 10) 1946.

Ice cream used in this study contained 12 per cent fat. Ten samples of coffee, of maple and of vanilla ice cream were assayed for carotene, riboflavin and reduced ascorbic acid content. The results were uniform for the three flavors. The average for carotene was 0.1 mg. and for riboflavin 0.26 mg., per hundred grams. No ascorbic acid was detected, probably because of the large amount of air incorporated in commercial ice cream to increase its bulk.

Eggs are considered one of the richest food sources of riboflavin. Commercial grade whole eggs contain about 0.2 mg. of riboflavin per hundred grams; thus, they are not so rich in this vitamin as the ice cream under discussion.

According to Cheldlin and Williams (Pub. No. 4237, Galveston, Texas, University of Texas, 1942), such common foods as beef round, pork loin, veal chop, leg of lamb, mutton shoulder, chicken leg and oysters contain about the same amount of riboflavin as was present in the ice cream under discussion, but these authors discovered much less riboflavin in whole wheat bread, chicken breast, salmon, dried lima beans, cabbage and carrots, which are widely used foods. Hodson (*Food Research* **5**:395, 1940) studied the riboflavin content of about fifty fruits and vegetables. Of these only one, broccoli, approached ice cream in riboflavin value, and only six or eight of the others contained half as much riboflavin.

GENGENBACH, Denver.

EFFECT OF WAR AND SIEGE IN BUDAPEST ON ITS INFANTS AND CHILDREN. G. SURÁNYI and Ö. KERPEL-FRONIUS, Orvosok lapja **1**:150 (Oct.) **1945.**

The siege of Budapest lasted fifty days; it began Dec. 24, 1944, and ended Feb. 12, 1945. During this time Budapest's whole population was crowded into cellars. The siege of the city came unexpectedly, and the inhabitants were not prepared for it. Since children and babies could not be bathed, the purulent cutaneous infections (impetigo, furunculosis and others) were widespread and their healing slow and difficult. Scurvy was not observed. It was interesting that an influenza epidemic did not develop among the crowded people. Infants fed mother's milk remained alive, while most of the infants fed artificially with different mixtures of carbohydrates or with potato soups died of starvation, especially those under the age of 6 months. Babies who had overcome these bad conditions became atrophic and many of them died later of dysentery.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

THE CAMPAIGN AGAINST RICKETS IN HUNGARY. T. BIELEK and K. WALTNER, Orvosok lapja **1**:310 (Nov.) 1945.

The prophylactic campaign against rickets was started in Hungary in 1941 and grew in scope from year to year. Twenty-five thousand pregnant mothers received vitamin D, and the same vitamin was given to 70,000 babies in 1944. Twice, once during October and once in February, vitamin D was given to the infants in form of injections. Every effort was made after the war to continue the prophylaxis against rickets. For the coming winter of 1945-1946, enough vitamin D for injection was stored to provide sufficient doses for 71,500 infants.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

VITAMIN C CONTENT OF THE MILK IN BUDAPEST IN 1945. P. VÉGHELYI, Orvosok lapja **2**:203 (Feb.) 1946.

Véghelyi examined with the method of Bessey the vitamin C content of various samples of cow's milk in 1936 in Budapest. Their vitamin C content was between 1.20 and 1.50 mg. per hundred cubic centimeters. In 1945 he examined 15 different samples of milk and stated that most of the samples showed no trace of vitamin C and that the highest level was 0.80 mg. per hundred cubic centimeters. The cow's milk in this year contained so little of the vitamin that infants had to be fed supplementary tablets constantly.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

INFANT MORTALITY IN 1945 IN BUDAPEST. Ö. KERPEL-FRONIUS, Orvosok lapja **2**:597 (May) 1946.

The infant mortality rate at the Child Clinic in Budapest, Hungary, was 21 per cent in 1942, while in 1945 it grew to 46 per cent. After the battle of Budapest, mothers had no milk to feed their children. Since artificial food was not at hand, infants were nourished only with carbohydrate mixtures and potatoes, which caused underfeeding and atrophy. Many infants died from inanition. Mortality would have been even higher had not the American Military Mission, International Red Cross and the Swedish, the Swiss and the Danish Red Cross sent evaporated milk and drugs which saved many of the infants. In the month of August improvement was remarkable, for the infant mortality rate sank rapidly until it reached the level of October 1942.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

Newborn

OTITIS MEDIA OF THE NEWBORN. E. LEVY-SOLAL, M. LELONG, R. JOSEPH and J. DEBAIN, Presse méd. **54**:25 (Jan. 19) 1946.

The authors present 11 cases of otitis media in newborn infants, 4 of them in premature or debilitated infants. No symptom of disease of the upper respiratory tract was apparent; in several of the infants the ear drums appeared practically normal. The infant with otitis media eats poorly and loses weight, but the temperature remains normal or descends below normal. After paracentesis, appetite returns and gain in weight is resumed. In several of these infants, antrotomy was necessary. The authors stress the necessity for otoscopic examination and paracentesis for any newborn infant who is eating poorly and fails to gain weight.

DAFFINEE, Melrose, Mass.

ALTERATIONS IN HEMOPOIESIS IN FETAL ERYTHROBLASTOSIS. U. TEODORI, Riv. di clin. pediat. **44**:353 (June) 1946.

The author reviews the known facts concerning fetal erythroblastosis (in its three manifestations of fetal hydrops, acute yellow atrophy of the liver [icterus gravis] and congenital hemolytic anemia), which show that the disease is apparently due to the action of maternal antibodies toward fetal antigens.

The concept that all manifestations of erythroblastosis are simply a consequence of a state of hemolysis is criticized. It is a fact that the degree of erythroblastosis is in no way proportionate to the anemia and that the alterations in hemopoiesis show a pronounced tendency to anaplasia, involving also at times the formation of the white blood cells. It must, therefore, be admitted that there is a pathologic response of the hemopoietic organs to the increased destruction of the blood cells. The author suggests the hypothesis that the action of the maternal antibodies on the fetal antigens is not limited to hemolysis but extends its influence to the cells of the liver and the reticuloendothelial system. From this originate the alteration in hemopoiesis and, in the various types of erythroblastosis, the pathologic changes in the water level and the bilirubin metabolism. The hemolytic action, however, is not important in the intrauterine life but increases greatly in significance after birth; thus, the fact that anemia becomes much more serious in those infants who do not die rapidly and sometimes survive is explained.

FROM THE AUTHOR'S SUMMARY.

RETINAL HEMORRHAGE IN THE NEWBORN AND ITS CAUSES. JIRI JIRMAN, Pediat. listy **1**:117, 1946.

Twelve hundred newborn babies were examined within a few hours after birth, and in 478 retinal hemorrhages were observed. These hemorrhages are caused by the diapedesis of red blood corpuscles as the direct consequence of asphyxia of the fetus in utero and during labor. The method of delivery is irrelevant. Retinal hemorrhages were also observed in infants delivered by cesarean section. This is contrary to the opinion of McKeown and Spencer, who considered the increased intracranial pressure due to the application of instruments on the head of the fetus the only cause of these hemorrhages.

FROM THE AUTHOR'S SUMMARY.

SERUM IRON AND SERUM BILIRUBIN LEVELS IN CONGENITAL ANEMIA OF THE NEWBORN AND ICTERUS GRAVIS NEONATORUM. BO VAHLQUIST, Upsala läkaref. förh. **50**:183 (May 1) 1945.

The author studied 4 cases of congenital anemia and 5 cases of icterus gravis neonatorum as to the levels of serum iron and serum bilirubin. Serum iron was

determined according to the Heilmeyer and Plötner method, serum bilirubin according to the method of Jendrassik and Cleghorn. It was observed that the serum iron level in congenital anemia at first was high and later fell to normal. In icterus gravis the serum iron value sometimes was low or normal, in other cases levels were high. The serum bilirubin value in congenital anemia was normal. In icterus gravis the value was very high in several cases, but other cases showed only slightly higher levels than the highest recorded in physiologic icterus neonatorum. The hyperbilirubinemia regressed rapidly in the 2 cases with recovery.

Only the direct van den Bergh reaction gave positive results in the 4 cases of congenital anemia of the newborn and in 4 of the 5 cases of icterus gravis, while the indirect method gave negative results. The author contends that the van den Bergh reaction cannot be regarded as decisive in distinguishing between hepatogenic and hemolytic jaundice during the newborn period.

WALLGREN, Stockholm, Sweden.

Acute Contagious Diseases

COMBINED VACCINATION AND THE PROTECTION OF INFANTS AND THE GENERAL POPULATION AGAINST INFECTIOUS DISEASES. G. RAMON, Pédiatrie **35**:21 (Jan.-Feb.) 1946.

After a brief historic review in which the author traces the origin of immunization to France and gives credit to the pioneer work done in America, he cites statistics from the United States, England and France proving the value of immunization procedures in the armed forces, as well as in the civilian population. After pointing out the remarkable preventive results of immunization during the last war, Ramon praises the value of combined vaccination against diphtheria, tetanus and the typhoid-paratyphoid group. He emphasizes the practical angle of combined immunizations and the fact that they have a reenforcing action on each other. He mentions the antidiphtheria-antitetanus combination as used in the United States; the diphtheria, tetanus and typhoid-paratyphoid vaccination as used in France; the tetanus-typhoid-paratyphoid vaccination as used in the Canadian, Portuguese and Swiss armies; the combinations of diphtheria, tetanus, typhoid, paratyphoid and typhus (Rickettsia) as used in the French army in North Africa, and the diphtheria-pertussis combination as used in the United States. A rather large body of data, as well as a list of references, is given to prove the effectiveness of immunization procedures. It is emphasized that the treatment of small or large groups is not sufficient, but that every person should be reached by these procedures. Ramon quotes his own statement made in 1939 expressing his fear of outbreaks of diphtheria epidemics because of migration of population and large concentrations of children. Again quoting his own statement of 1940, he praises the reduction of morbidity and mortality due to vaccinations, and, at the time of this article, he deplores the fact that vaccinations were not carried out in accordance with the law in large parts of the population during the war years. He states:

"Vaccination against diphtheria was made compulsory by law in 1938 and against diphtheria and tetanus in 1940 for children from 1 to 14 years of age. Furthermore, the triple vaccination was made compulsory for persons between the ages of 10 and 30 years living in areas menaced by typhoid fever."

In the closing part of the article, the author makes detailed suggestions as to distribution and posology of the vaccines. In general, he suggests three injections of 0.5 to 2 cc. each within two weeks, with a "booster shot" at the age of 6 months, or one year after the initial injection. In case of injury or the occurrence of typhoid or diphtheria epidemics, he suggests an immediate booster shot. The

emphasis laid on typhoid immunization and the superficial mention of pertussis immunization are in interesting contrast to the recommendations and practices in the United States.

GLASER, Chicago.

RECURRENCE OF ACUTE ANTERIOR POLIOMYELITIS: REPORT OF A CASE. G. MOURIQUAND, N. BOULEZ and R. MARAL, Pédiatrie **35**:48 (Jan.-Feb.) 1946.

Mouriquand and his associates briefly report the case history of a 4 year old child who had, they state, two attacks of poliomyelitis. The first occurred at the age of 13 months, with paralysis of the right arm, the second one three years later, affecting the left arm and right leg. The child had received a smallpox vaccination three weeks prior to the second attack. There were cases of poliomyelitis in the community at the time of the second attack.

The case is of interest because it permits several interpretations and stimulates discussion on controversial subjects.

1. Remissions of poliomyelitis are rare, but recurrences are still more exceptional.

2. With the localized condition in one arm, was the immunity from the first attack too low to protect the patient from a second infection?

3. Was the second infection exceptionally powerful?

4. According to Levaditi ("Précis de Virologie," page 43), postvaccinal encephalitis is a central nervous system localization of a latent infection during the favoring stage of allergy. Perhaps a latent poliomyelitis infection could have become active owing to this vaccination.

GLASER, Chicago.

ANTIDIPHTHERITIC STAPHYLINE—A NEW ANTIBIOTIC. R. DULISCOUET, Presse méd. **53**:653 (Dec. 1) 1945.

All forms of the staphylococcus seem to possess some antibiotic powers, but one strain of larger size is particularly efficacious. The author presents the results of his experiments using the staphylococcus against the organisms of diphtheria. Apparently, a substance is produced which inhibits the growth of the diphtheria bacillus but which has no effect on toxins already produced.

DAFFINEE, Melrose, Mass.

PRESENT TREATMENT OF DIPHTHERIA. JAROSLAV PROCHAZKA, Pediat. listy **1**:120, 1946.

An account of the present day treatment of diphtheria in the fever department of the Bulovka Hospital in Prague, Czechoslovakia, is given.

FROM THE AUTHOR'S SUMMARY.

RELATION OF HERPES ZOSTER TO CHICKENPOX. KARL V. KUNDRATITZ, Wien. klin. Wchnschr. **58**:349 (June 28) 1946.

The author reviews the historical and experimental evidence of the relationship between these two virus diseases. He reminds one that the renowned Hungarian pediatrician, Johann von Bókay, during practically his entire lifespan, from 1888 to 1928, studied, clarified and published his observations on the relationship of herpes zoster to chickenpox.

A great mass of clinical evidence has closely associated the two diseases. As Kundratitz wisely concludes, until virus research has so progressed that the technic for the identification of a specific virus can be easily carried out, further clarification of the relationship between herpes zoster and chickenpox will be impossible.

ABT, Chicago.

PNEUMONIA COMPLICATING MEASLES IN CHILDREN REPATRIATED FROM THE DUTCH INDIES: ISOLATION OF MEASLES VIRUS AND HEMOPHILUS INFLUENZAE FROM THE LUNGS. N. LUBSEN and J. D. VERLINDE, Nederl. tijdschr. v. geneesk. **91**:250 (Feb. 1) 1947.

The serious cases of pneumonia observed in children repatriated from the East Indies who had contracted measles while on board ship are described. In 1 patient on whom a postmortem examination was done seventeen days after the onset of the exanthem, laryngitis, tracheitis and mucopurulent bronchitis were observed, together with extensive bronchopneumonia. One of the authors was able to isolate from the lungs a virus that was almost completely identical with a virus isolated from the blood of a patient with measles on the first day of the exanthem. In the lungs, also, Hemophilus influenzae and nonhemolytic streptococci were demonstrated. This explains the fact that these patients did not react favorably to penicillin and sulfathiazole.

VAN CREVELD, Amsterdam, Netherlands.

Acute Infectious Diseases

AN EPIDEMIC OF INFLUENZA B IN AUSTRALIA. F. M. BURNET, J. D. STONE and S. G. ANDERSON, Lancet **1**:807 (June 1) 1946.

An epidemic of influenza B in which good serologic studies were made is described. Schools and rural districts were particularly involved. Influenza A was also present in the population. Of particular interest were 2 persons both of whom within the space of two weeks were attacked by influenza A and B. This may be taken as evidence that there is no overlapping of immunity to the two viruses in man.

HODGES, Cleveland.

STAPHYLOCOCCIC TOXOID—TEN YEARS OF THERAPY. G. RAMON, R. RICHOU, P. MERCIER and G. HOLSTEIN, Presse méd. **53**:677 (Dec. 15) 1945.

Observations on 3,000 cases showed the validity of treatment of staphylococcus infections with staphylococcus toxoid. In veterinary medicine also the toxoid has been efficacious. Toxoid theoretically is superior to penicillin in staphylococcus infections because it induces an increase of the natural defenses of the body against the infection.

DAFFINEE, Melrose, Mass.

PROTHROMBIN TIME IN INFANTS WITH MALARIA OR LEISHMANIASIS. P. PINNA, Riv. clin. pediat. **44**:606 (Oct.) 1946.

The author, considering the frequency of hemorrhages in cases of malaria and leishmaniasis, in which the reticuloendothelial system and particularly the liver and the spleen are steadily infected, examined the prothrombin time in children with these diseases.

He observed the prothrombin time to be nearly normal in children with malaria and considerably lengthened in those with leishmaniasis. The author states his belief that the difference in reaction in the two diseases depends on the diverse behavior of the reticuloendothelial system, which certainly appears more active in children with leishmaniasis. He also expresses his opinion that prothrombin could in many cases be elaborated by the reticuloendothelial system itself.

FROM THE AUTHOR'S SUMMARY.

THE SPREAD OF TYPHOID FEVER IN CHILDREN IN THE BRNO AREA IN 1945. B. DOKULIL and J. D. VYMETAL, Pediat. listy **1**:41, 1946.

The course of an epidemic of typhoid fever in 140 children is described. The use of blood transfusions, in addition to currently suggested treatment, is recommended.

FROM THE AUTHORS' SUMMARY.

Chronic Infectious Diseases

PULMONARY TUBERCULOSIS IN INFANTS. A. DUFOURT, Pédiatrie **35**:30-33 (Jan.-Feb.) 1946.

The author begins the article with a reference to Ranke's stages of development of tuberculosis. He states that the division into stages is not only of academic interest but of greatest importance from the point of view of treatment of the patient and protection of others. He is of the opinion that in France the problem of exogenous reinfection has been neglected, whereas in other countries more attention has been paid to it. The author points out that, while usually the prime infection of tuberculosis is benign in children, in the first two years of life, however, it is serious, perhaps because of continuous reinfection by contact. He expresses his belief that the picture of tuberculosis has been changed during the last twenty or thirty years as pneumonias and caseous bronchopneumonias of the primary infection type have disappeared. This may be attributable to dispensaries and organizations for case finding in the home. In spite of the good results, much remains to be improved in these organizations.

In discussing these stages, the author first speaks of the primary infection, which may pass completely unobserved or be found on routine roentgenographic examination or autopsy. Although most physicians are of the belief that the disease in children at this stage is not contagious, the author is convinced that according to bronchoscopic findings virulent organisms are present and much greater care is indicated. Important in children are cases of epituberculosis, which may be either acute and febrile or afebrile and extend over several months. On the basis of bronchoscopic examination, epituberculosis was found to consist of a congestive edema affecting the lungs and the bronchi. On such examination one does not find Koch bacilli. The author states his opinion that this reaction is on an allergic basis. In general, these cases of epituberculosis are benign and pneumothorax is contraindicated, as it will produce adhesions between the leaves of the pleura which will prevent effective collapse therapy, if necessary, after ten years or more. Chronic epituberculosis is a more serious condition, evidently caused by secondary external infection and leading frequently to caseous bronchopneumonia. It is also called caseous inflammatory epituberculosis and may terminate in cavern formation.

The author states that children may show cavernous tuberculosis as a result of primary infection, or they may, after an incubation period of several years, show cavities as typical findings of tertiary tuberculosis. The period between primary and tertiary lesions in children is a longer one—five to ten years—than in adults—two to three years or less. Children who have had pleurisy or who show signs of secondary tuberculosis in the apical region of the lungs have a particular tendency to tertiary tuberculosis. The origin of apical tuberculosis, according to the author, is a broken-down ganglion which spreads virulent bacilli through the lymphatics into the blood stream and through the heart into the lungs. It is, therefore, wrong to believe a child protected from tertiary tuberculosis after healing of the primary infection of the lungs if one neglects the condition of the lymph glands. Tertiary tuberculosis demands collapse therapy. Rest will not cure this child, even though the lesion may temporarily regress.

GLASER, Chicago.

CUTANEOUS HYPERSENSITIVITY TO TUBERCULIN. G. PAISSEAU, Presse méd. **54**:130 (March 2) 1946.

A child 3 years of age entered the hospital because of primary tuberculosis. A cutaneous test (Pirquet) was done, and a decidedly positive reaction developed. At the same time, a generalized eruption occurred, with papular lesions remarkably similar to the positive reaction. Two large nodules also appeared on

the anterior surfaces of the lower part of the legs, undistinguishable from the lesions of erythema nodosum. Macules were present over the entire body.

The lesions gradually regressed, and cutaneous reactions were tested using higher dilutions of tuberculin. When the dilutions of 1:250 and 1:100 were reached, a positive reaction was obtained, and the nodules on the legs flared up. With the use of undiluted tuberculin, a strongly positive reaction was obtained and a generalized eruption occurred, with a flare-up of many of the former lesions. The clinical condition of the child in the meantime had improved steadily.

DAFFINEE, Melrose, Mass.

CUTANEOUS REACTION TO TUBERCULIN AND GRANULOCYTIC DIAGNOSIS. R. BENDA and D. A. URQUIA, Presse méd. **54**:373 (June 15) 1946.

The authors contend that by the study of granulocytic morphology a more accurate and earlier diagnosis of tuberculosis may be obtained. The pathologic granulocyte is characterized by the presence of numerous granules, unequal in size, irregular in shape and often massed together. Such granulocytes appear before the cutaneous reaction becomes positive. A series of observations on these granulocytes will serve to determine the course of a tuberculous infection, while the cutaneous reaction will not be of assistance.

DAFFINEE, Melrose, Mass.

AMINO ACID BLOOD CURVE IN PULMONARY TUBERCULOSIS IN CHILDREN. UBALDO PELLEGRINI, Riv. clin. pediat. **45**:18, 1947.

The author studied the curve for the amino acid level in the blood after intravenous injections of aminoacetic acid as an expression of hepatic function in 25 children with active pulmonary tuberculosis. In 21 patients, the liver was affected to a variable degree. In 4 children, the hepatic function was normal. There is not always a comparison between the extent of the tuberculous lesions and abnormal hepatic function.

FROM THE AUTHOR'S ABSTRACT.

SO-CALLED HYPERERGIC UNEQUAL PIRQUET REACTION (MEYERHOFER). FRANTISEK BLAZEK, Pediat. listy **1**:29, 1946.

In the research department of the Second Children's Clinic unequal Pirquet reactions were studied in 258 tuberculous children. Of the children 74.4 per cent showed unequal reactions. The position of the arm had little influence on the resulting reaction. It was impossible to prove any relation between the inequality of the reaction and the activity of the process (as measured by red blood cell sedimentation rate) because the correlation quotient was only $+0.084 + 0.043$. The unequal reaction developed parallel to the allergy during the course of tuberculous infections. This was confirmed by the correlation between the degree of allergy and the inequality, the quotient being $+0.16 + 0.04$. The most pronounced unequal reactions occurred in recent secondary infiltrations, disseminative processes and, particularly, in specific pleurisy with effusion. Primary or secondary infiltrations with caseation showed unequal reactions in three fourths of the cases. Slightly less frequently this type of reaction occurred in the primary complex and hilar adenitis in the stage of healing. It is impossible to draw any conclusions as to the further course of the tuberculous process from the inequality of the reaction. Since hyperergic unequal Pirquet reactions occur so frequently in recent secondary infiltrations, disseminative and caseous lesions, one has to look on them as warning signs and pay particular attention to those patients.

FROM THE AUTHOR'S SUMMARY.

PRIMARY TUBERCULOUS INFECTION IN THE COURSE OF MALARIA. JAROSLAV LHOTAK, Pediat. listy **1**:122, 1946.

In a 10 year old boy with tuberculous hilar adenitis, who returned from China, the quotidian form of malaria developed. The symptoms disappeared after treatment with quinine. But fourteen days later pleurisy with interlobar effusion developed. The effusion was quickly absorbed. This paper throws more light on the relation of tuberculosis to malaria.

FROM THE AUTHOR'S SUMMARY.

Diseases of Blood, Heart and Blood Vessels and Spleen

ANASTOMOSIS OF THE AORTA TO A PULMONARY ARTERY IN CERTAIN TYPES OF CONGENITAL HEART DISEASE. WILLIS J. POTTS, SIDNEY SMITH and STANLEY GIBSON, J. A. M. A. **132**:627 (Nov. 16) 1946.

A new operation providing a direct anastomosis between the aorta and a pulmonary artery (the left) is described. The purpose of the operation is identical with that of the Blalock operation, namely, to relieve the anoxemia in certain types of congenital cardiac disease. This operation has the advantage of not sacrificing the innominate or the subclavian artery. It also allows the operator to decide on the size of the anastomotic opening, although the most advantageous size has not been determined as yet. The operation is made possible through the use of a specially designed clamp which permits the flow of a substantial amount of blood through the aorta while a portion of it is pinched off for surgical treatment. The operation is a difficult one. Full details are given. Three patients are reported on. The 2 children who survived the operation were tremendously benefited.

BAIRD, Wauwatosa, Wis.

CHANCES OF SURVIVAL IN VON JAKSCH-HAYEM-LUZET ANEMIA. G. CAREDDU, Riv. di clin. pediat. **94**:721 (Dec.) 1944.

The author, after briefly summing up the evolution of medical knowledge on familial erythroblastic (Cooleys') anemia, calls attention to the fact that in differential diagnosis one can perhaps still speak of von Jaksch-Hayem-Luzet splenic anemia, but only in those cases in which familial erythroblastic anemia, as well as Di Guglielmo's erythroblastosis, can be excluded. A notable contribution to differential diagnosis is the determination of hemoglobin, resistance and the measurements of red blood cells, as even in initial and vague cases these data are sufficiently definite to substantiate other clinical findings.

FROM THE AUTHOR'S ABSTRACT.

UNUSUAL CONGENITAL CARDIAC DEFECT. LUCIANO DE LA VILLA RODRIGUEZ, Rev. cubana pediat. **18**:608 (Oct.) 1946.

This is a study of a newborn baby with cyanosis but no heart murmur who died at 3 days of age. At the autopsy, only one ventricle was observed. It was in communication, on the one hand, with the right auricle through the only existing auriculoventricular orifice, and, on the other hand, with an arterial vessel which was divided into the aorta and the pulmonary arteries. The left auricle was in communication with the one ventricle. The author gives an interesting discussion of the imperfect development of the heart, outlining the development in this case and explaining the anomalies as secondary atrophy of the left chambers.

KEITH, Rochester, Minn.

UNEQUAL DISTRIBUTION OF CYANOSIS IN CONGENITAL CARDIAC DISEASES. IVAN HECKO, Pediat. listy **1**:8, 1946.

From observation on 2 cases of congenital cardiac diseases, which were subsequently seen at autopsy, the author is of the opinion that constantly more pronounced cyanosis of the upper part of the body develops in uncomplicated transposition of the large vessels, whereas prevalence of cyanosis of the lower part of the body suggests a stenosis of the aortic isthmus situated above a widened and persistent ductus arteriosus (botalli).

FROM THE AUTHOR'S SUMMARY.

Diseases of Nose, Throat and Ear

LARYNGO-TRACHEO-BRONCHITIS: A STATISTICAL REVIEW OF 549 CASES. E. A. MORGAN and D. E. S. WISHART, Canad. M. A. J. **56**:8 (Jan.) 1947.

A statistical review of 549 patients with laryngotracheobronchitis admitted to the Hospital for Sick Children, Toronto, Canada, from 1926 to 1944, is presented. A steady increase in admissions, from 8 in 1928 to 55 in 1944, was noted. The mortality rate was in inverse proportion to the number of patients admitted: 75 per cent died in 1928 to 9.2 per cent in 1944. Of the patients, 69 per cent were under 2 years of age and only 5 per cent were over 6 years old.

From a bacteriologic point of view, the patients were classified into three main groups: those with virus infections, those with bacterial infections and those having primary virus with secondary bacterial infection. Treatment consisted of placing the child in a steam tent, administration of sulfonamide drugs or penicillin and pentobarbital sodium U. S. P. (nembutal®) and use of suction to remove mucous plugs. With increased difficulty in breathing, tracheotomy after passage of a small bronchoscope or an intratracheal catheter is advised. Special postoperative care is outlined.

The principal causes of death were failure to relieve obstruction, overwhelming toxemia, postoperative infection, pneumothorax and mediastinal emphysema. Of all deaths 87 per cent were in children under 4 years of age.

MOORE, Omaha.

THE SPEECH BEHAVIOR OF INFANTS WITHOUT FAMILIES. ARTHUR J. BRODBECK and ORVIS C. IRWIN, Child Development **17**:145 (Sept.) 1946.

A group of 95 orphanage infants ranging from 1 day to 6 months in age, was compared with a group of family infants of the same age range in terms of two measures of speech behavior: phoneme type and phoneme frequency. The purpose was to learn whether during the first half year of life differences between the groups are present. It was found that:

1. A graphic comparison showed that the means for the orphanage infants fell below those of the family infants at all age levels and for both type and frequency measures.

2. More than half (58 per cent) of the differences in phoneme type proved to be reliable, but only one of the measures of phoneme frequency was satisfactory.

3. Differences in consonant type were reliable at all age levels, and differences in type for the crying data, with vowel and consonant sounds combined, became progressively reliable with increase in age.

4. When the data on family infants were broken down into those for professional and unskilled family groups, and again compared with data on the orphanage infants, the means for the orphanage infants were observed to deviate from the means of both family groups several times more than those for either of the two

socioeconomic groups deviated from each other, especially for those measures which showed reliable differences between the orphanage and family groups as a whole previously.

PALMER, Wichita, Kan.

INFANT SPEECH: VOWEL AND CONSONANT FREQUENCY. ORVIS C. IRWIN and HAN PIAO CHEN, J. Speech Disorders **11**:123, 1946.

Ninety-five infants from birth to 2.5 years of age were studied in the derivation of equations for vowel and consonant frequencies during these years. Two equations are needed to express the development of vowel frequency. The first, which includes the first two years of life, is $Vt = 0.69A + 51.8$. The second equation is $Vt = 11.78A^{0.5}$. The equation derived from the means of consonant frequency is $Ct = 12.5 * 0.134A$. This forms an exponential curve. Throughout the first thirty months of life the frequency of vowel sounds exceeds that of consonant sounds. At the first bimonthly period, vowel sounds occur about five times more frequently than consonant sounds and not until the last two month period is their occurrence approximately the same. The processes of development for vowel and consonant frequency are radically different. It is reasonable to assume that these three equations express the laws of the development of phonemic frequency during infancy.

PALMER, Wichita, Kan.

Diseases of Lungs, Pleura and Mediastinum

PENICILLIN THERAPY IN CHRONIC BRONCHIAL ASTHMA. HOWARD C. LEOPOLD, J. Allergy **17**:166 (May) 1946.

Penicillin was used intramuscularly in a group of patients with chronic bronchial asthma. All known treatment of the condition had been tried previously, without success. The penicillin was given every four hours, for a minimum of 240,000 units a day for a varying number of days, the shortest period being seven days. One patient received treatment over forty-five days. Administration of penicillin failed to clear permanently the signs and symptoms of perennial chronic bronchial asthma of the infectious type.

There was partial relief in 32 per cent of the patients with infectious asthma. No change in the type or number of organisms cultured from the sputum resulted from treatment in 81 per cent of the cases.

HOYER, Cincinnati.

TREATMENT OF ASTHMA WITH RECTAL SUPPOSITORIES OF AMINOPHYLLINE AND SODIUM PENTOBARBITAL. SAMUEL J. PRIGAL, ABNER M. FUCHS and PHILIP M. SCHULMAN, J. Allergy **17**:172 (May) 1946.

Adult suppositories containing 0.5 Gm. of aminophylline and 0.1 Gm. of pentobarbital sodium were used in treatment of 47 patients with asthma. Relief during an attack of asthma was obtained in 44 of the patients in five to thirty-five minutes.

A child's suppository, containing 0.025 Gm. of aminophylline and 0.05 Gm. of pentobarbital sodium, was used with 4 children, ranging from 2 to 13 years of age. Relief was obtained in ten to twenty minutes.

SEROLOGIC REACTIONS IN PRIMARY ATYPICAL PNEUMONIA. ALFRED L. FLORMAN and ALICE B. WEISS, J. Lab. & Clin. Med. **30**:902 (Nov.) 1945.

Specimens of serum from 68 patients with the clinical diagnosis of primary atypical pneumonia were subjected to one or more serologic tests. The authors used the cold agglutinin test, the indifferent streptococcus agglutinin test, the elementary body type of complement fixation and the Kahn flocculation and Kolmer complement fixation tests for syphilis. Of these patients, 63 per cent had positive reactions to the cold agglutinin test; 47 per cent, positive reactions to the indifferent

streptococcus agglutinin test; 26 per cent, positive reactions to the elementary body type of complement fixation test, and 17 per cent, transitory positive reactions to the Kahn and Kolmer tests. The results were significantly different from those obtained from 32 control sets of serums. These tests serve the practical purpose of more clearly defining the disease, although the etiologic agent for the majority of cases of primary atypical, or virus, pneumonia is unknown.

WILKINSON, Galveston, Texas.

PULMONARY HAEMOSIDEROSIS. DONALD PATERSON, Proc. Roy. Soc. Med. **39**:131 (Jan.) 1946.

A girl 6½ years of age had been in good health until she was 18 months old, when she had an attack of bronchitis requiring admission to the hospital. On roentgenograms the chest had the appearance of miliary tuberculosis. At 2 years of age attacks of breathlessness occurred which were diagnosed as asthma. As she grew older, the attacks became less severe, but she remained pale, her hemoglobin content ranging from 30 to 70 per cent. In September 1945 she became rapidly more anemic and was readmitted to the hospital. Physical examination on her admission showed pronounced pallor and poor nutrition. The liver and the spleen were just palpable; the tonsils were enlarged, but there was no generalized glandular enlargement. Roentgenograms of the chest showed a fine, mottled appearance of the lungs, spreading almost to the periphery. Transfusion was given, but her red blood cell count during the next three weeks fell from 5,000,000 to 3,000,000 cells per cubic millimeter. Sternal puncture showed normal bone marrow. Nucleated cells totaled 86,000 per cubic millimeter. The differential cell count is given in the paper. The evidence pointed to the presence of a hemolytic process but not to acholuric jaundice, since the cell fragility was normal. In the hope that it might be possible to avert further hemolytic episodes, her spleen was removed, but with no improvement.

In the author's opinion, this case was one of pulmonary hemosiderosis, as shown by mottled appearance of the chest on roentgenograms, which persisted for five years, the refractory anemia, a biopsy of the lung which showed numerous hemosiderin-filled macrophages and the history of hemoptyses.

WILLIAMSON, New Orleans.

LACTESCENT EFFUSIONS IN THE PLEURA OF INFANTS. S. LEVI, Riv. di clin. pediat. **44**:473 (Aug.) 1946.

The author presents a survey and reelaboration of all cases in the literature of lactescent effusions of the pleura in infants, with a description of 2 personal cases. The whole subject matter is revised and rearranged.

FROM THE AUTHOR'S SUMMARY.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

NEW OBSERVATIONS ON ACTION OF EPINEPHRINE IN THE PYLORIC SYNDROME OF INFANCY. A. INGIULLA, Riv. di clin. pediat. **40**:681 (Nov.) 1942.

Ingiulla reported in the *Rivista di Clinica Pediatrica* **40**:13 (Jan.) 1942, abstracted in the *American Journal of Diseases of Children* **75**:414 (March) 1948, that the oral administration of 2 to 5 drops of epinephrine before each feeding had relieved the vomiting of children with pylorospasm and pyloric stenosis. He now reports on 5 additional children for whom the treatment was successful. In the pediatric clinic in Florence, Italy, it has been possible to eliminate the necessity for laparotomy and surgical treatment of pyloric stenosis.

HIGGINS, Boston.

CHEMOTHERAPY IN INFANTILE DIARRHEA. JOSEF SVEJCAR, K. KUBAT AND M. TUTTER, Pediat. listy **1**:153, 1946.

The authors report on a series of 136 cases of diarrhea in infants up to the age of 1 year, treated partly with only sulfaguanidine or succinylsulfathiazole (sulfasuccidine)• and partly with these drugs in combination with penicillin. In this series are 20 newborn and 15 premature infants. Ten had diarrhea of enteric origin without toxic signs, while 12 had toxic signs. Thirteen infants showed signs of infectious colitis and 61 infants had diarrhea due to parenteral infections. Of these last, 30 infants showed toxic symptoms and in 5 infants who were originally treated for dyspepsia a recurrence of diarrhea developed.

The mortality rate in this series of treated infants was 6.6 per cent, i. e., 9 died. Seven of these had toxic parenteral diarrhea (2 were brought into the hospital in a moribund condition), 1 was a newborn infant and 1 a premature infant.

Sulfaguanidine or succinylsulfathiazole was used for all the children. The initial dose was 10 × 0.25 Gm., i. e., 2.5 Gm. the first day. One half of this dose was used during the following days, usually for five days. There were no untoward toxic effects.

Penicillin was used in addition to this treatment in premature infants, in newborn infants, in those who showed relapses and in infants with serious toxicity or in whom the parenteral infection was severe. The dosage was 40,000 international units daily, divided into eight intramuscular injections.

The effect of the treatment was noticeable, partly in the quick return of the stools to normal, but even more so in rapid hydration, which meant that the use of intravenous infusions could be reduced. In infants for whom infusions had to be used, they became more effective. The authors are of the opinion that this is the effect of sulfonamide action on the Escherichia coli flora of the proximal parts of the intestine.

Penicillin limited and attenuated parenteral infections and eliminated their noxious influence on digestion, factors which became evident in the steady increase in weight.

In consequence of the good results of the aforementioned treatment, dietetic therapy in diarrheal diseases becomes less important, schematic and monotonous. The authors stress the importance of the sterility of the milk foods used because of the danger of superimposed exogenous infection of the intestinal tract.

FROM THE AUTHORS' SUMMARY.

A DIAPHRAGMATIC HERNIA IN AN INFANT: REPORT OF A CASE. KAMIL KUBAT and MILOSLAV TUTTER, Pediat. listy **1**:172, 1946.

This infant was cyanotic from birth. It was admitted to the hospital on the seventeenth day after birth. A diaphragmatic hernia was found on the left side. The patient died three days afterward. The whole of the small intestine and part of the large intestine were found in the thoracic cavity. The clinical picture and, in particular, the diagnosis of this disease are discussed and surgical treatment in suitable cases is suggested.

FROM AUTHORS' SUMMARY.

Nervous Diseases

POREncephaly. EUGENE P. PENDERGRASS and CHARLES R. PERRYMAN, Am. J. Roentgenol. **56**:441 (Oct.) 1946.

Porencephaly, as described by LeCount and Semerak, is a defect of brain substance communicating with the ventricles or separated from them by a thin layer of cerebral tissue and covered on the outside by the arachnoid. Theirs is, perhaps,

the most widely accepted definition. The origin of the defect may be classified as developmental or acquired. Gene abnormalities, injury of germ plasm before fertilization or congenital vascular defects may cause the developmental type. The acquired factors may appear in prenatal or postnatal life and may be classified as traumatic, vascular and inflammatory. The underlying causation is usually difficult to establish. According to Wilson, the acquired type is cystic rather than crateriform, does not always lead to ventricular fenestration, may contain yellowish albuminous fluid and is not lined by smooth gyral formation, but by a membranous wall adherent to the white matter of the centrum semiovale. None of the authors' 16 patients who were operated on or autopsied fulfilled all Wilson's criteria for the developmental type of porencephaly.

Porencephaly is a benign condition; its differentiation from mass and contracting lesions is most important. Occasionally, it is confused with other cystic lesions.

The authors studied 29 patients with encephalographic or ventriculographic methods. Sixteen were subjected to craniectomy. The average age was 16; the youngest was 9 months and oldest 34 years of age. The duration of symptoms varied from three months to thirty years. The commonest complaint was epilepsy. The numerous symptoms and findings are presented and discussed.

Conventional roentgenograms may be normal in appearance, but frequently some asymmetry is evident. This is most commonly due to a change in the thickness of the skull on one side which may be localized or diffuse. The bone on the affected side may be thick or thin. The cranial vault may be smaller on the affected side and accompanied by numerous bony changes. The authors report, for the first time, calcification in the region of the porencephaly.

Encephalography or ventriculography must be used for definite diagnosis. It is pointed out that twenty-four examinations may be necessary to demonstrate an existing porencephaly. Ventriculography is preferred in patients with increased intracranial pressure. If there has been incomplete drainage of the cerebrospinal fluid prior to the injection of air, there will be partial visualization of the porencephaly.

The examination should include the following positions: (1) posteroanterior and anteroposterior views; (2) each lateral erect, (3) each lateral in the prone position using a vertical beam; (4) a single lateral in the supine position (brow up), and (5) a single lateral in the prone position (brow down) using a horizontal beam. If drainage is incomplete, further views may be necessary.

Roentgenologically, the various types of porencephaly are classified as "lobe," "interlobe" and "hemisphere." Other types of atrophy which may be associated with this condition include cortical or subcortical atrophy, enlargement of the lateral ventricles and increase in size of the subarachnoid pathways. These defects may be homolateral, contralateral or bilateral and localized or generalized. There is usually a shift of the ventricles toward the porencephalic side but displacement may be to the opposite side.

The authors discuss cases with roentgenologic and pathologic illustrations.

HARRISON, Chicago.

News and Comment

GENERAL NEWS

Pediatric Residency Established for Training in Neoplastic Diseases.—Memorial Hospital Center for Cancer and Allied Diseases, New York, has established a residency in pediatrics.

The period of service is a minimum of six months and its purpose is to train the pediatrician in the diagnosis and management of neoplastic diseases in childhood. The resident will also participate in the research program in progress at the Sloan-Kettering Institute. Three months' credit toward requirements for pediatric residency training has been approved by the American Board of Pediatrics.

For further particulars applicants may communicate with the director, Pediatric Service, Memorial Hospital Center for Cancer and Allied Diseases, 444 East Sixty-Eighth Street, New York 21.

Physicians Certified by the American Board of Pediatrics.—The following physicians were certified as specialists by the American Board of Pediatrics after examinations held at St. Louis, Feb. 18, 19 and 20, 1949.

Eugene W. Austin, Evansville, Ind.; Curtis A. Beerman, Johnstown, Pa.; Milton Carl Bessire, Abilene, Texas.; Richard Charles Brown, Owosso, Mich.; Joseph A. Browning, Warren Ohio; Cho Duke Choy, Chicago; Harold S. Cole, Rutherford, N. J.; Clyde Douglas Conrad, Charleston, S. C.; James T. Cowart, Tampa, Fla.; Harry M. Estes, Nashville, Tenn.; Matthew Feldman, River Edge, N. J.; Paul M. S. Fischer, Ann Arbor, Mich.; Samuel W. Gollub, St. Louis; William Burton Greenberg, West New York, N. J.; Caldwell K. Hamilton, St. Louis; Olga Romanov Hoffman, New York; S. Sprigg Jacob, East Lansing, Mich.; Max Kaplan, Denver; Robert Emmett Keeley, Chicago; Howard L. Lange, Belleville, Ill.; Sidney S. Marder, St. Albans, N. Y.; Beryl M. McDonald, Rockford, Ill.; Luther L. McDougal Jr., Tupelo, Miss.; Conn Lewis Milburn Jr., Cleveland; James Urban Morrison Jr., New Orleans; Herbert F. Philipsborn Jr., Glencoe Ill.; Elliott Podoll, Louisville, Ky.; Ivan J. Roggen, Saginaw, Mich.; Wendell Linwood Severy, Los Angeles; Vincent Arthur Spinelli, Yonkers, N. Y.; LeRoy J. Stephens, St. Louis; Edward Louis Strem, St. Paul; John D. Stull, Olney, Ill.; James Mack Sutton Jr., Albany, Ga.; Edward H. Townsend Jr., Rochester, N. Y.; Robert Warner, Buffalo; Erle Ewing Wilkinson, Nashville, Tenn., and James N. Yamazaki, Cincinnati.

Book Reviews

Polycories (Storage Diseases). By Robert Debré. Price, 215 francs. Pp. 126, with no illustrations. Paris, France: G. Doin & Cie, 1947.

This monograph represents a thorough discussion of the storage diseases, a rare but interesting group of metabolic disturbances. The author, who has done considerable original work in this field judging from his extensive list of publications, proposes the term "polycories," of Greek origin and meaning "much saturation," and defines the diseases as characterized by the excessive accumulation of substances that occur normally in the organ-specific cells, due to a constitutional neurohormonal disturbance. In the clinical description, the author uses as a source his own observations, showing for example, photographs of a child observed from the sixth to the twentieth year of life, as well as reports from the literature. He describes the laboratory findings in detail and uses graphs to explain the chemical behavior of the metabolic functions of the organs involved.

Discussed are the glycogen and fat storage diseases of the liver, with brief mention of the involvement of other organs, glycogen storage diseases of the heart and the disturbances of the fat and glycogen content of the organs in diabetes. Diagnosis, prognosis, pathologic anatomy and chemistry are discussed in separate chapters, followed by consideration of the pathogenesis and pathologic physiology. Attention is attracted to several cases of pyloric stenosis, in which histologic sections of the muscle showed a similar appearance as the heart muscle in glycogen storage diseases, and to the disturbed glycogen metabolism in cases of cyclic vomiting and vomiting of pregnant women.

In the chapter on treatment, the author suggests that the administration of the glycogenotropic hormone of the pituitary gland may be therapeutically effective, but it is not available in pure form. He discusses on a theoretic basis several other possibilities of treatment based on the hormonal deficiency theory. The last chapter deals with chemical, histologic and therapeutic methods of diagnosis. The bibliography consists of a collection of literature from all over the world, arranged alphabetically and according to chapters. There is difficulty at times in finding references mentioned in the text and some of them seem to be omitted in the bibliography.

The book deals thoroughly with a highly controversial problem; the material presented is certainly of value to men active in research in this field and may serve occasionally as a reference for the practitioner.

Phtisiologie Infantile. By Pierre Lowys. Preface by Prof. R. Debré. Price 2,120 francs. Pp. 716, with 220 illustrations. Paris, France: Editions Médicales Flammarion, 1947.

A monograph of 716 full-sized pages devoted entirely to the subject of tuberculosis in children must, by its extent alone, be a rather complete work, which this book is in most respects. Some of the more recent developments in the field of diagnosis and therapy are, however, not included, and their absence probably calls for a supplement or an early new edition of the book in order to maintain its value for the practicing physician. Pulmonary calcifications due to fungous infections have been reported in increasing number in the more recent literature but are not

given consideration in the chapter on differential diagnosis. Much space is devoted to the chapter on therapy, describing several methods which now are almost entirely of historical value alone; the more modern attempts of chemotherapy and antibiotic therapy are unfortunately not included. This is an understandable shortcoming, as the book was probably prepared before the latest developments came into the medical literature, but it is neverthless a regrettable lack and decreases the value of the book for the practitioner.

The work and opinions of many investigators are quoted in the monograph, but, in the author's words, "the number and variety of subjects treated prohibit a bibliography." The large number of case reports and roentgenograms obtained from the sanatorium Le Roc des Fitz, of which the author is medical director, greatly enriches the book by bringing the theoretic problems closer to the comprehension of the practicing physician. The quality of the reproduction of the roentgenograms, however, leaves much to be described and is a definite shortcoming in a book of this type.

Melk; in het bijzonder als zuigelelingenvoedsel. Second edition. By J. H. De Haas, M.D., and I. O. Meulemans. No price listed. Pp. 112, with many charts and graphs. Batavia: Tweede Druk, 1947.

The postwar edition of this text on milk has been revised to include some of the lessons reemphasized by the stress of starvation, isolation and shortages. The preeminence of milk as an infant food constrained the authors to keep the work up to date.

In reference style are included the composition of cow's milk, colostrum, human milk and others. Various forms of preserved milk and milk by-products are described. The descriptions of vitamin and mineral ingredients include briefly their functions. Mention is made of the relative frequency of vitamin A, B, C and D deficiencies compared with the European and American incidence. Additions required to produce optimum vitamin intake are described.

Present knowledge of the chemical composition of inorganic elements of human and cow's milk is included.

Readers are aided in transposing figures of composition by tables in both metric and English systems. References and an index complete the work.

Textbook of Bacteriology: The Application of Bacteriology and Immunology to the Diagnosis, Specific Therapy and Prevention of Infectious Diseases for Students and Practitioners of Medicine and Public Health. By Hans Zinsser. Ninth edition, revised by David T. Smith, M.D., and others. Price $10. Pp. 992, with 246 illustrations. New York: Appleton-Century-Crofts, Inc., 1948.

This time-honored text has been not only revised but extensively rewritten. After a lapse of nine years without a revision, the necessity for a thorough reconsideration of old material and the addition of much new material was seriously undertaken by the authors, for which they should be congratulated. The chapters on medical mycology, which were never adequate in previous editions, together with the added and greatly expanded sections on pleuropneumonia organisms, viruses, sulfonamide drugs, antibiotic substances and immunology, are probably the most noteworthy and welcome changes.

It is encouraging to note the greater emphasis placed on the public health aspects of bacteriology, which is in keeping with the present tendency to expanded teaching of preventive medicine.

It is with great relief that the many new illustrations have been noted. The text contains a large amount of material that was published in the literature only a few months before the book itself was printed. This is a compliment to both the authors and the publishers.

If any criticism can be made, it might be directed at the inadequate and half-hearted attempt at setting out certain important words in boldface type. Many of these words are poorly chosen, and the effort is incompletely carried out. A large book of this type tends to become a reference book and not a real text. A more liberal treatment with phrases or whole sentences in boldface type could make the book useful both as a reference or textbook in its complete form and as a rapid review of essential subject material most desperately needed, especially by students of the medical sciences. An improvement of this sort is desirable to curb the tendency toward writing outlines or synopsis series.

Otitis media en el lactante: Estudio fisiopatológico y clinico. By Manuel Fairén Guillén. No price given. Pp. 382, with 125 illustrations. Zaragoza, Spain: Revista española le pediatría, 1947.

This book is the result of the experience of the author with 567 children with otitis media, on whom 330 paracenteses were performed. The remainder of the children were treated by chemotherapy. An excellent discussion is given of the anatomic relations, etiologic factors, bacteriologic and pathologic aspects and the symptoms, forms, diagnosis and treatment of the disease.

Although written in Spanish, the well chosen charts and illustrations, the clear text and the immense experience of the author make this a worth while book on the subject.

Actualités de médecine infantile. By G. Doin & Cie. No price given. Pp. 346, with 7 illustrations. Paris, France: 1948.

This book was written in honor of Prof. P. Rohmer, head of the pediatric department of the Universití de Strasbourg Faculté de Médicine since 1923. It consists of a collection of articles covering subjects in many fields of current pediatric interest. The articles either concern the problems of everyday practice or are discussions of conditions of rare occurrence or controversial nature. The authors are outstanding authorities in their fields from Belgium, Egypt, France, the Netherlands, Italy, Yugoslavia, Spain, Sweden and Switzerland.

The 29 articles deal with topics in the fields of public health, infectious diseases and antibiotic substances, genetics, chemotherapeutics, vitamin, water and mineral metabolism, child psychiatry, infant feeding, hematology, rheumatic fever, tuberculosis, urology and others. Some of the articles lack desirable detailed information, as might be expected from their shortness and the range of subject matter they try to cover; others, however, are interesting as to the ideas brought forth and are quite adequate in the information they give on the subject. References to the literature are given in only a few articles in sufficient detail to be of help to someone wishing to read further. Every physician interested in the management of diseases in childhood will find this book a valuable part of his private library, as it offers the opinions of well known authors on interesting, rare or controversial subjects.

Le syndrome de diabète rénal avec rachitisme ostéomalacique incurable et troubles du développment chez l'enfant. By Robert Debré. Price, 145 francs. Pp. 64, with 5 illustrations. Paris, France: G. Doin & Cie, 1947.

The syndrome discussed in this monograph is most frequently associated with the names of Debré, de Toni and Fanconi. It consists of renal diabetes, intractable rickets with osteomalacia and deficiency in development, particularly in height; there is an associated acidosis without ketosis, disturbances of renal function and hypophosphatemia. The onset is usually in early infancy, but a later form with an onset between the third and fifth year is also known.

The presentation covers the historical recognitions, clinical descriptions of the early and late types, the underlying changes in body chemistry, the pathologic anatomy and the physiologic pathologic modifications. These are discussed, also, in relation to other similar syndromes. There is a timely warning of the danger to these patients of glucose tolerance tests, as they frequently suffer a hyperglycemic shock during such tests, which may be fatal. The hypophosphatemia is contrasted to the hyperphosphatemia in renal rickets. The possible relationship to a disturbance in cystine metabolism, or the syndrome of Lignac, is considered in detail. The author disagrees with those who are of the opinion that the metabolic and associated anatomic changes in cystinosis may bring about the syndrome under discussion. He leans, rather, toward the belief that both syndromes, together with that of renal rickets, may have a common origin in constitutional defects of the vegetative nervous system.

The large amount of material is well organized, and Debré's French is pleasing and easily understood. There is no index, but the subdivisions of the chapters are given in the table of contents. There is a full bibliography with brief commentary on each article.

Fatty Liver Disease in Infants in the British West Indies. Medical Research Council, Special Report Series 263. By J. C. Waterlow. Price, 2s. Pp. 84, with 2 illustrations. London: His Majesty's Stationery Office, 1948.

This monograph is a study of a syndrome observed in infants in the British West Indies. The main features seen were edema, muscular wasting and fatty infiltration of the liver. Additional symptoms characteristic of so-called infantile pellagra were never severe and often absent. The disease differed in this respect from a condition known as kwashiorkor met in West Africa, which, it is suggested, is the same disease complicated by various avitaminoses.

Fatty liver disease is characterized by the presence of fatty infiltration of the liver, high mortality and resistance to treatment by ordinary dietary measures. Accurate data are not available, but, on the basis of this study, the author suggests that a diet consisting mainly of carbohydrate with little milk is the main cause of the syndrome. Infants studied revealed on their admission to the hospital a weight below normal, gross muscular wasting but only incomplete loss of subcutaneous fat, enlarged liver and, sometimes, glossitis and angular stomatitis. Edema was present in all. There was no correlation among loss of weight, avitaminosis and the severity of the hepatic damage.

Fifteen infants were studied for this preliminary report, and intensive investigations were carried out. No adequate etiologic factor was found other than a diet high in carbohydrate and low in protein. The edema was considered to be due to hypoproteinemia. A specific feature of the disease was that the

hepatic fat was exogenous in source, whereas in wasting diseases it is endogenous. This occurs in experimental animals only when there is a relatively high caloric intake. The author is of the opinion that signs of this disease are similar to those seen in infants dying of undernutrition, and that one condition can be converted into the other by increasing or decreasing the caloric intake.

Treatment with vitamins, choline or methionine had no effect. On the other hand, a high milk intake had a good therapeutic result.

The author notes that cirrhosis of the liver in children occurs often in the part of the West Indies where fatty liver disease is commonest. He suggests that this disorder may be an aftermath of fatty liver disease.

Breast Feeding: A Guide to the Natural Feeding of Infants. By F. Charlotte Naish, B.Ch. (Cantab.). Price, $3.50. Pp. 164, with 20 illustrations and 10 tables. New York: Oxford University Press, 1948.

This little book contains many needed principles and much practical information concerning breast feeding, which in America, in many quarters, has become a lost art. Most outstanding is the chapter on the "Mind of the Mother." The author, herself a mother of five children and a physician of experience, writes convincingly of the mental change a woman experiences after childbirth: how she is incapable of making decisions and is subject to the loudest and strongest arguments in regard to breast feeding.

The ill advised early use of formulas in hospitals and the almost universal impatience with breast feeding in those infants who do not take to it in the first four days are discussed. Nurses should be taught that feedings during the first four days are only practice. There should be a period of about two hours each day when the baby may lie with the mother. Sound reasons are presented for using both breasts at each feeding. The third to the sixth weeks are considered the danger weeks, and all the common pitfalls in nursing are discussed, including the attitudes of relatives and friends and the use of complementary feedings, which should be given with a spoon from a saucer.

Weaning should not start until after the fifth month, and it should be a gradual process lasting at least two months. Pediatricians should consult farmers more frequently to get their basic principles, especially in the art of hand expression of milk. The obstetrician should read the section on mastitis and abscess of the breast and not always recommend that a mother should stop breast feeding when either of these conditions is present.

Besides its richness in information, the book is well written and should be read by every one caring for infants.

Directory of Pediatric Societies *

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President: Dr. Armando de Arruda Sampaio.
First Secretary: Dr. Luis Fontoura y Lauro Machado Oliveira, Caixa Postal 2103, São Paulo, Brazil.
Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.
Time: Twelfth of every month, 8:30 p. m.

Asociación Pediatrica de Guatemala

President: Dr. Carlos Manuel Monzon, Plazuela Santuario de Guadalupe, Guadalupe.
Secretary: Dr. Maria Isabel Escobar, Casa del Niño no. 1, Guadalupe.

British Paediatric Society

President: Dr. H. T. Ashby, 13 St. John St., Manchester, England.
Joint Secretary: Prof. Alan Moncrieff, Hospital for Sick Children, Great Ormond St., London W. C. 1.
Place: Windermere.

Bulgarian Pediatric Society

President: Dr. L. Ratchew, University Children's Hospital, Wassil Kolarow 46, Sofia.

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* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Chinese Pediatric Society

President: Dr. W. S. Fu, The Shanghai Public Hospital for Children, 11 Hsiang Shan Road, Shanghai, China.
Secretary: Dr. T. F. Su, The Shanghai Public Hospital for Children, 11 Hsiang Shan Road, Shanghai, China.
Time: Concurrent with the annual conference of the Chinese Medical Association.

Czechoslovak Pediatric Society

Chairman: Prof. Dr. Jiri Brdlík, 2 Sokolská, Prague II.

Danish Pediatric Society

President: Prof. E. Lenstrup, Copenhagen.
Secretary: Dr. Gjørup, Dronning Louises Børnehospital, Copenhagen.

German Pediatric Society

President: Dr. H. Kleinschmidt.
Secretary: Dr. F. Goebel, 5 Moorenstrasse, Düsseldorf, Germany (British Zone).
Place: Düsseldorf. Time: September 1949.

Indian Pediatric Society

President: Dr. K. C. Chaudhuri, 56/2 Creek Row, Calcutta 13.
Secretary: Dr. N. G. Mojumdar, 148 Russa Rd., Calcutta 26.
Place: 67 Dharamtala St., Calcutta 13. Time: Every second and fourth Wednesday of each month.

Nederlandsche Vereeninging voor Kindergeneeskunde

President: Dr. J. L. Keyzer, 114 St. Josephstr., Tilburg.
Secretary: Dr. H. Reerkink, % Sophia Kinderziekenhuis, 160 Gordelweg, Rotterdam.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

Palestine Jewish Medical Association, Section of Physicans of Children's Diseases

President: Prof. L. F. Meyer, 29 Toelsohn St., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

Pediatric Society of New Zealand

President: Dr. Lawrence Ludbrook, The Lister Building, Victoria Street East, Auckland.

Royal Society of Medicine, Section for the Study of Diseases in Children

President: Prof. J. M. Smellie, 5 Flat, 8 Bolingbroke Grove, London S. W. 11.
Secretary: Dr. Mary Wilmers; Dr. R. Bonham Carter.
Place: 1 Wimpole St., London W. 1. Time: Fourth Friday of each month, 4:15 p. m.

Schweizerische Gesellschaft für Pädiatrie

President: Prof. Dr. A. Hottinger, Petersplatz 12, Basel.
Secretary: Dr. F. Hauser, Kinderspital, Basel.

Sociedad Boliviana de Pediatria

President: Dr. Carlos Ferrufino, Casilla 272, La Paz, Bolivia.
Secretary: Dr. Cecilio Abela D., Casilla 272, La Paz, Bolivia.
Place: S. C. I. S. P. Bldg. Time: Every Thursday.

Sociedad Chilena de Pediatria

President: Mr. Raúl Matte, Santiago, Chile.
General Secretary: Dr. Mariano Latorre, Santiago, Chile.
Place: Medical Society, Santiago, Chile. Time: 7:30 p. m., weekly.

SOCIEDAD CUBANA DE PEDIATRIA

President: Prof. Agustin Castellanos.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21, Apartado 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedes y Hospital Municipal de Infancia, Habana. Time: 9 p. m., last Wednesday of every month.

SOCIEDAD DOMINICANA DE PEDIATRIA

President: Dr. Alberto Peguero, Avenida Bolivar 117, Ciudad Trujillo, R.D.
Secretary-Treasurer: Dr. Jaime Jorge, Lea de Castro 19, Ciudad Trujillo, R.D.
Place: Children's Ramfis Hospital. Time: 8 p. m., last Friday of every month

SOCIEDAD ECUATORIANA DE PEDIATRIA

President: Dr. Alfredo Ceballos Carrión.
Secretary: Dr. Rafael Compte Andrade, P. O. Box 3480, Guayaquil.
Place: Hospital Central. Time: 11:30 a. m., every Friday.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Jesus Avarez de los Cobos.
Secretary: Dr. Luis Torregrosa F.
Place: Hospital Infantil. Time: Last Thursday of every month.

SOCIEDAD DE PEDIATRÍA DE CONCEPCIÓN (CHILE)

President: Dr. Raúl Ortega A., Hospital Clínico Regional, Concepción.
Secretary: Dr. Fidel Urrutia, Hospital Clínico Regional, Concepción.
Place: Hospital Clínico Regional, Concepción. Time: 7:30 p. m., second Tuesday of every month from April to December, inclusive.

SOCIEDAD DE PEDIATRÍA DE CÓRDOBA

President: Dr. Juan Francisco Herrera, Córdoba, Argentina.
Secretary: Dr. Albino F. Dottori, Dean Fumes 2000, Esq. Ocaña (N.), Córdoba, Argentina.
Place: Comite pro Defenso del Niño, Dean Fumes 2000, Córdoba, Argentina.
Time: Once a month.

SOCIEDAD DE PEDIATRIA DEL LITORAL

President: Dr. Jose E. Celoria, Hospital Centenario, Rosario, Argentina.
Secretary: Dr. Gloria Lovell, Hospital Centenario, Rosario, Argentina.

SOCIEDAD DE PEDIATRÍA DE SANTIAGO DE CUBA

President: Dr. Antonio Béguez César, Sagarra 107, Santiago de Cuba.
Secretary: Dra. Susana Texdó Vaillant, Padre Pico 57, Santiago de Cuba.
Place: Colegio Médico. Time: Last Tuesday of every month.

SOCIEDADE PORTUGUÊSA DE PEDIATRIA

President: Prof. Almeida Garret.
Secretary: Dr. Cordeiro Ferreira, Hospital de D. Estefania, Lisbon.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Pastor Oropeza, Caracas.
Secretary: Dr. Guillermo Flores, Chacin, Sur 17, no. 26-2, Caracas.
Place: Hospital Municipal de Niños, Caracas. Time: Once a month.

SOCIEDAD YUCATECA DE PEDIATRIA

President: Dr. José Lavalle, Yucatan, Mexico.
Secretary: Dr. Francisco Solís, Yucatan, Mexico.
Place: Hospital del Niño, Yucatan, Mexico.

Société de Pédiatrie de Paris

President: Dr. G. Heuyer, 1 Ave. Emile Deschanel, Paris 7e, France.
Secretary: Dr. Maurice Lamy, 94 rue de Varenne, Paris 7e, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

Societé Polonaise de Pédiatrie

President: Dr. Jan Bogdanowicz, Dzialdowska 1, Warsaw.
Secretary: Dr. Zofia Leimbach, Mieroslawskiego 9 m.6, Warsaw.

South African Paediatric Association

Chairman: Dr. Basil Melle, 89 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.
Secretary-Treasurer: Dr. Seymour Heymann, 17 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.

Swedish Association of Pediatrics

President: Prof. A. Lichtenstein, Crown Princess Louise's Children's Hospital, 30 Polhemsgata, Stockholm.
Secretary: Dr. K. A. Melin, Farjestadsvägen 16, Ängby.

Swedish Medical Society, Section for Pediatrics and School Hygiene

President: Dr. R. Hybbinette, Kommendorsgatan 3, Stockholm.
Secretary: Dr. B. Broman, Eriksbergsgatan 1A, Stockholm.
Place: Various clinics and hospitals in Stockholm and Uppsala. Time: Second Friday of each month (except summer).

Uruguayan Socety of Pediatrics

President: Dr. Héctor C. Bazzano.
Secretary: Dr. José M. Portillo.
Place: Club Medico del Uruguay, Avenida Agraciada 1464 (Piso 13), Montevideo.

Vienna Pediatric Society

President: Prof. Dr. A. Solé, Karolinen-Kinderspital, Sobieskigasse 31, Vienna 9.
Secretary: Doz. Dr. Asperger, Universitäts-Kinderklinik, Lazarettgasse 14, Vienna 9.

NATIONAL

American Medical Association, Scientific Assembly. Section on Pediatrics

Chairman: Dr. Woodruff L. Crawford, 321 W. State St., Rockford, Ill.
Secretary: Dr. Margaret Mary Nicholson, 1801 Eye St. N. W., Washington, D. C.
Place: Atlantic City, N. J. Time: June 6-10, 1949.

American Academy of Pediatrics

President: Dr. Warren R. Sisson, 319 Longwood Ave., Boston 15.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Annual Meeting: Place: San Francisco. Time: Nov. 14-17, 1949.

American Hospital Association, Massachusetts Hospital Association

Chairman: Dr. Frank Wing, Boston.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly 79, Mass.

American Pediatric Society

President: Dr. Valjean Cooke, 8700 Argyle Ave., St. Louis.
Secretary-Treasurer: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.
Place: Atlantic City. Time: May 3-5 (?), 1949.

Canadian Society for the Study of Diseases of Children

President: Dr. P. E. Williams, 193 James St. S., Hamilton, Ontario.
Secretary-Treasurer: Dr. R. L. Denton, 1615 Cedar Ave., Montreal.

Society for Pediatric Research

President: Dr. Sidney Farber, 300 Longwood Ave., Boston.
Secretary: Dr. Robert Ward, Bellevue Hospital, New York 16.

SECTIONAL

Intermountain Pediatric Society

President: Dr. Spencer Snow, 75 S. Main St., Salt Lake City.
Secretary-Treasurer: Dr. Esther Gross, 202 E. South Temple St., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

New England Pediatric Society

President: Dr. Howard W. Brayton, 179 Allyn Street, Hartford 3, Conn.
Secretary-Treasurer: Dr. Harry Shwachman, 300 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Three meetings a year, occurring from September to May.

North Pacific Pediatric Society

President: Dr. Clarence L. Lyon, 407 Riverside Ave., Spokane 8, Wash.
Secretary: Dr. Aldis B. Johnson, 515 Cobb Bldg., Seattle, Wash.

Northwestern Pediatric Society

President: Dr. Paul Bancroft, 909 Sharp Bldg., Lincoln, Neb.
Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Rocky Mountain Pediatric Society

President: Dr. William D. Rothwell Jr., Republic Bldg., Denver.
Secretary: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.
Place: Children's Hospital of the Colorado General Hospital. Time: Monthly from October to June.

Southern Medical Association, Section of Pediatrics

Chairman: Dr. Carroll M. Pounders, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Samuel F. Ravenel, 371 N. Elm St., Greensboro, N. C.

STATE

Alabama Pediatric Society

President: Dr. W. A. Daniel Jr., 115 S. Union St., Montgomery 5, Ala.
Secretary-Treasurer: Dr. D. B. Monsky, 905 Norman Bridge Rd., Montgomery 6, Ala.
Place: Montgomery, Ala. Time: September 1949.

Arizona Pediatric Society

President: Dr. Hugh Thompson Jr., 110 S. Scott St., Tucson, Ariz.
Secretary: Dr. James R. Sickler, Physicians Bldg., Tucson, Ariz.
Place: Phoenix or Tucson. Time: On call.

Arkansas State Pediatric Association

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

California State Medical Society, Section on Pediatrics

Chairman: Dr. Alice Potter, 1418 Ninth Ave., San Francisco 22.
Secretary: Dr. Carl Erickson, 595 E. Colorado, Pasadena.

Florida State Pediatric Society

President: Dr. Edgar W. Stephens, 910 Harvey Bldg., West Palm Beach.
Secretary: Dr. Hugh A. Carithers, 2000 Park St., Jacksonville 4.
Place: Concurrent with state association convention and fall meeting.

Georgia Pediatric Society

President: Dr. Lee Bivings, 20 Fourth St. N. W., Atlanta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Place: Atlanta. Time: At time of annual state meeting.

HEZEKIAH BEARDSLEY PEDIATRIC CLUB OF CONNECTICUT

President: Dr. H. L. F. Locke, 179 Allyn St., Hartford, Conn.
Secretary: Dr. L. W. Minor, 119 Main St., Middletown, Conn.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Eugene T. McEnery, 4458 W. Madison St., Chicago 24.
Secretary: Dr. George L. Drennen, Jacksonville, Ill.
Place: Palmer House, Chicago. Time: May 10-12, 1949.

INDIANA STATE PEDIATRIC SOCIETY

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Matthew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

IOWA PEDIATRIC SOCIETY

President: Dr. Charlotte Fisk, 1201 Equitable Bldg., Des Moines 9.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.
Place: Des Moines. Time: April 1949.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. William C. Rivenbank, 1448 Louisiana Ave., New Orleans 15.
Secretary-Treasurer: Dr. Bertha Wexler, 3439 Prytania St., New Orleans 15.
Place: New Orleans. Time: May 7, 1949.

MEDICAL SOCIETY OF THE STATE OF NEW YORK, PEDIATRIC SOCIETY

Chairman: Dr. Thurman B. Givan, 115 Remsen St., Brooklyn 2.
Secretary: Dr. Reginald A. Higgons, Port Chester.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION

Chairman: Dr. Waldo E. Nelson, Temple University, Philadelphia 40.
Secretary: Dr. Carl C. Fischer, 100 W. Coulter St., Philadelphia 44.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. H. J. Lewis, 2956 Biddle Ave., Wyandotte.
Secretary: Dr. Robert H. Trimby, 122 W. Hillsdale, Lansing.

MISSISSIPPI STATE PEDIATRIC SOCIETY

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Place, Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. George Clark, 1817 Vinton St., Omaha.
Secretary-Treasurer: Dr. Michael Crofoot, 1407 Medical Arts Bldg., Omaha 2.
Place: Children's Memorial Hospital. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW HAMPSHIRE PEDIATRIC SOCIETY

President: Dr. Thomas B. Walker, Porthmouth.
Secretary-Treasurer: Dr. Ursula G. Sanders, Concord.

NEW JERSEY MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Israel J. Wolf, 231 E. 31st St., Paterson.
Secretary: Dr. N. T. Crane, 147 E. 7th St., Plainfield, N. J.

NEW MEXICO STATE PEDIATRIC SOCIETY

President: Dr. M. K. Wylder, 221 W. Central Ave., Albuquerque.
Secretary-Treasurer: Dr. Ly Werner, 221 W. Central Ave., Albuquerque.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Samuel F. Ravenel, 371 N. Elm St., Greensboro, N. C.
Secretary: Dr. Charles H. Gay, 1523 Elizabeth Ave., Charlotte, N. C.

NORTHERN CALIFORNIA PEDIATRIC SOCIETY

President: Dr. William C. Deamer, 3 Fifth Ave., San Francisco 18.
Secretary: Dr. A. L. Gleason, 1066 Longridge Rd., Oakland 10.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

Oklahoma State Pediatric Society

President: Dr. J. B. Snow, 625 N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

Philippine Pediatric Society

President: Dr. Alberto V. Tupas, Philippine General Hospital, Manila, Philippines.
Secretary: Dr. Artemio P. Jongco, Philippine General Hospital, Manila, Philippines.
Place: Philippine General Hospital. Time: Every two months.

South Carolina Pediatric Society

President: Dr. B. Owen Ravenel, 95 Rutledge Ave., Charleston 16.
Secretary-Treasurer: Dr. John R. Harvin, 206 N. Sumter St., Sumter.

Tennessee Pediatric Society

President: Dr. W. O. Vaughan, 2103 Hayes St., Nashville 5.
Secretary-Treasurer: Dr. C. Barton Etter, 1678 Peach, Memphis 12.
Place: Chattanooga. Time: Second Monday in April.

Texas Pediatric Society

President: Dr. John K. Glen, 4412 Montrose St., Houston.
Secretary-Treasurer: Dr. James N. Walker, 3616 Tulsa Way, Fort Worth 7.
Place: San Antonio. Time: Oct. 7-8, 1949.

Virginia Pediatric Society

President: Dr. C. P. Brown, 142 W. York St.. Norfolk.
Secretary: Dr. E. Berkeley Neal, 303 Washington Ave. S. W., Roanoke.

West Virginia State Medical Society, Section on Pediatrics

President: Dr. Thomas G. Folsom, 1139 Fourth Ave., Huntington.
Secretary: Dr. Warren J. Parsons, 425 Eleventh St., Huntington.

Wisconsin State Medical Society, Section on Pediatrics

Chairman: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee 2.
Secretary: Dr. L. M. Simonson, 1001 N. 8th St., Sheboygan.

LOCAL

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. John Hart Davis, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. Francis F. Silver, 9400 Euclid Ave., Cleveland.
Place: Allen Memorial Medical Library. Time: 8:15 p. m., October, December, February and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. A. L. Chute, 170 St. George St., Toronto, Canada.
Secretary: Dr. John Fletcher, 262 St. Clair St. W., Toronto, Canada.
Place: Academy of Medicine. Time: 8:30 p. m., third Thursday of each month.

Baltimore City Medical Society, Pediatric Section

Chairman: Dr. Charles O'Donovan Jr., 5 E. Read St., Baltimore.
Secretary: Dr. T. Campbell Goodwin, 16 E. Biddle St., Baltimore.

Bronx Pediatric Society

President: Dr. Harry S. Pizer, 1726 Davidson Ave., New York.
Secretary: Dr. William A. Schonfeld, 211 W. 106th St., New York 25.
Place: Morrisania City Hospital. Time: 8:30 p. m., second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. Walter R. Coles, 604-2d St., Brooklyn.
Secretary: Dr. Bernard Benjamin, 845 Park Pl., Brooklyn 16.
Place: Granada Hotel. Time: 8:45 p. m., fourth Wednesday of February, March. April, October and November.

Buffalo Pediatric Society

President: Dr. Douglas P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

Central New York Pediatric Club

President: Dr. T. Wood Clarke, 7 Cottage Place, Utica.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Tuesday of April and October.

Chicago Pediatric Society

President: Dr. John L. Reichert, 1791 Howard St., Chicago 26.
Secretary: Dr. Alvah L. Newcomb, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May inclusive.

Cincinnati Pediatric Society

President: Dr. John H. Hunt, Kemper Lane Bldg., Cincinnati.
Secretary: Dr. William F. Hunting, 6048 Montgomery, Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. Guy Hacker, 5711 Goliad St., Dallas.
Secretary-Treasurer: Dr. George R. Branch, 4325 Cole Ave., Dallas.
Place: Children's Hospital of Texas and Bradford Memorial Hospital. Time: 1 p. m., third Saturday and 8:30 p. m., the first Tuesday of each month.

Detroit Pediatric Society

President: Dr. Harold B. Rothbart, 773 Fisher Bldg., Detroit 2.
Secretary: Dr. S. S. Bernstein, 650 Maccabees Bldg., Detroit.
Place: Variable. Time: Five times annually.

Fort Worth Pediatric Society

President: Dr. Frank Cohen, 712 S. Henderson, Fort Worth, Texas.
Secretary: Dr. H. H. Womack, 1422 Pennsylvania, Fort Worth, Texas.
Place: Welch and West Restaurant. Time: Third Friday of each month.

Honolulu Pediatric Society

President: Dr. Donald Marshall, Medical Group, Honolulu.
Secretary-Treasurer: Dr. Teruo Yoshina, 1221 Victoria St., Honolulu

Houston Pediatric Society

President: Dr. Edward O. Fitch, 3720 Fannin St., Houston, Texas.
Secretary: Dr. Thomas J. Donovan, 3506 Sunset Blvd., Houston 5, Texas.
Place: River Oaks Country Club. Time: 7:30 p. m., last Tuesday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. Harry M. Gilkey, 1624 Professional Bldg., Kansas City.
Secretary: Dr. Leland Speer, 1022 Hoel Parkway, Kansas City.
Place: Kansas City General Hospital. Time: On call.

Knoxville-Oak Ridge Pediatric Society

President: Dr. Henry S. Christian, 205 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. John Eggleston, Oak Ridge Hospital, Oak Ridge, Tenn.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles 26.
Secretary-Treasurer: Dr. Robert Simonds, 267 S. Beverly Dr., Beverly Hills, Calif.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

MEDICAL SOCIETY OF THE COUNTY OF KINGS AND THE ACADEMY OF MEDICINE OF BROOKLYN, PEDIATRIC SECTION

President: Dr. Harold Levy, 750 St. Marks Ave., Brooklyn 16.
Secretary: Dr. Jacob J. Lichterman, 1433 Union St., Brooklyn 13.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month.

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION ON PEDIATRICS

President: Dr. John Washington, 2032 Belmont Rd. N.W., Washington, D. C.
Secretary-Treasurer: Dr. George Maksim, 1418 Good Hope Rd. S. E., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N.W. Time: Spring and fall.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. C. Barton Etter, 1678 Peach, Memphis 12, Tenn.
Secretary-Treasurer: Dr. Jacob Danciger, 188 S. Bellevue Blvd., Memphis 4, Tenn.
Place: University Center, 4 S. Dunlap. Time: 7 p. m., second Tuesday of every month.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. James Conway, 1721 E. Lake Bluff Blvd., Milwaukee 11, Wis.
Secretary-Treasurer: Dr. Walter Polacheck, 425 E. Wisconsin Ave., Milwaukee 2, Wis.
Place: City Club of Milwaukee. Time: Second Wednesday in February, April, June, October and December.

NASHVILLE PEDIATRIC SOCIETY

President: Dr. John M. Lee, Doctors Bldg., Nashville, Tenn.
Secretary: Dr. Dan S. Sanders Jr., 2103 Hayes St., Nashville, Tenn.
Time: Third Thursday of every month.

NEW YORK ACADEMY OF MEDICINE, SECTION ON PEDIATRICS

Chairman: Dr. John Dorsey Craig, 120 E. 75th St., New York 21.
Secretary: Dr. Morris Greenberg, 143 W. 87th St., New York.
Place: New York Academy of Medicine, 2 E. 103rd St. Time: Second Thursday of each month from November to May, inclusive, 8:30 p. m.

OKLAHOMA CITY PEDIATRIC SOCIETY

President: Dr. Bertha M. Levy, 717 N. W. 22d St., Oklahoma City 3.
Secretary: Dr. C. M. Bielstein, 301 N. W. 12th St., Oklahoma City 3.
Place: Oklahoma Club. Time: On call.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. Milton Rapoport, 741 S. 3d St., Philadelphia.
Secretary: Dr. D. Stewart Polk, W. Montgomery Ave., Rosemont, Pa.
Place: College of Physicians, 19 S. 22nd St. Time: 8:30 p. m., second Tuesday from October to May, inclusive.

PITTSBURGH PEDIATRIC SOCIETY

President: Dr. J. A. Gilmartin, 3708–15th Ave., Pittsburgh.
Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Municipal Hospital, Pittsburgh. Time: Second Friday in October, December, February and April.

QUEENS PEDIATRIC SOCIETY

Chairman: Dr. Walter C. A. Steffen, 42-28 Union St., Flushing, N. Y.
Secretary-Treasurer: Dr. Louis Appel, 33-03 Parsons Blvd., Flushing, N. Y.
Place: Forest Hills, N. Y. Time: Third Monday of October, February, April; first Monday of December.

RICHMOND PEDIATRIC SOCIETY

President: Dr. Thomas S. Chalkley, 421 W. Grace St., Richmond 20, Va.
Secretary-Treasurer: Dr. John Paul Jones, 810 W. Franklin St., Richmond 20, Va.
Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June, July and August.

ROCHESTER PEDIATRIC SOCIETY

President: Dr. Jerome Glaser, 85 San Gabriel Dr., Rochester 10, N. Y.
Secretary-Treasurer: Dr. Daniel B. Peeler, 1162 Lake Ave., Rochester 13, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee.
Time: Third Friday of each month from October to May.

ST. LOUIS PEDIATRIC SOCIETY

President: Dr. Merl J. Carson, 500 S. Kingshighway, St. Louis.
Secretary-Treasurer: Dr. Jackson K. Eto, 734 Missouri Theatre Bldg., St. Louis 3.
Place: Hotel Branscome. Time: Second Thursday of each month from October to May, inclusive, 6:30 p. m.

SAN ANTONIO PEDIATRIC SOCIETY

President: Dr. Lucius Hill, 328 Medical Arts Bldg., San Antonio 5.
Secretary-Treasurer: Dr. Edith M. Bonnet, 228 Medical Arts Bldg., San Antonio 5.
Place: Bexar County Medical Library. Time: 7:30 p. m., first Tuesday of every month.

SEATTLE PEDIATRIC SOCIETY

President: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle 1.
Secretary: Dr. Jack M. Doctor, 738 Broadway, Seattle 22.
Place: College Club. Time: Fourth Friday of each month from September to June at 6:30 p. m.

SOUTHWESTERN PEDIATRIC SOCIETY

President: Dr. Harry F. Dietrich, 416 N. Bedford Dr., Beverly Hills, Calif.
Secretary: Dr. Clement H. Maloney, Beverly Hills, Calif.
Place: University Club of Los Angeles. Time: 6:30 p. m., second Wednesday in January, March, May, September and November.

UNIVERSITY OF MICHIGAN PEDIATRIC AND INFECTIOUS DISEASE SOCIETY

President: Dr. Ernest H. Watson, University Hospital, Ann Arbor.
Secretary: Dr. Harry A. Towsley, 1313 E. Ann St., Ann Arbor.

WACO PEDIATRIC SOCIETY

President: Dr. M. C. Carlisle, 1410 Austin Ave., Waco, Texas.
Secretary: Dr. F. W. Hoehn, 1422 Austin Ave., Waco, Texas.
Place: Provident Hospital, 1725 Colcord, Waco, Texas. Time: Third Thursday of each month.

WESTCHESTER COUNTY MEDICAL SOCIETY, PEDIATRICS SECTION (NEW YORK)

President: Dr. Harry W. Kaessler, 147 Prospect Ave., Mount Vernon, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: The Roger Smith Hotel, White Plains, N. Y. Time: Fourth Thursday of every other month from September to June (dinner meetings).

WICHITA PEDIATRIC SOCIETY

President: Dr. C. T. Hinshaw, 105 S. Broadway, Wichita, Kan.
Secretary: Dr. R. A. Nelson, 209 E. Williams, Wichita, Kan.
Place: Variable. Time: First Thursday of each month.